

Списък на научните публикации

Научни публикации с импакт фактор:

1 F Stoyanov GS, Dzhenkov D, Ghenev P, Iliev B, Enchev Y, Tonchev AB. Cell biology of glioblastoma multiforme: from basic science to diagnosis and treatment. *Med Oncol* 2018;35(3):27 <https://doi.org/10.1007/s12032-018-1083-x> IF 2,634 za 2016

Abstract

First described in the 1800s, glioblastoma multiforme (GBM), a class IV neoplasm with astrocytic differentiation, as per the revised 2016 World Health Organization classification of tumors of the central nervous system (CNS) is the most common malignant tumor of the CNS. GBM has an extremely wide set of alterations, both genetic and epigenetic, which yield a great number of mutation subgroups, some of which have an established role in independent patient survival and treatment response. All of those components not only represent a closed cycle but are also relevant to the tumor biological behavior and resistance to treatment as they form the pathobiological behavior and clinical course. The presence of different triggering mutations on the background of the presence of key mutations in the GBM stem cells (GBMsc) further separates GBM as primary arising de novo from neural stem cell precursors developing into GBMsc and secondary, by means of aggregated mutations. Some of the change in cellular biology in GBM can be observed via light microscope as they form the cellular and tissue hallmarks of the condition. Changes in genetic information, resulting in alteration, suppression and expression of genes compared to their physiological levels in healthy astrocytes lead to not only cellular, but also extracellular matrix reorganization. These changes result in a multiform number of micromorphological and purely immunological/biochemical forms. Therefore, in the twenty-first century the term multiforme, previously outcast from nomenclatures, has gained new popularity on the background of genotypic diversity in this neoplastic entity.

Keywords Glioblastoma multiforme · Cell biology · Morphology · Genetics · Review

2 F Stoyanov GS, Kitanova M, Dzhenkov DL, Ghenev P. The diagnostic dilemma of epithelial marker expression in glioblastoma. *Pathol Oncol Res* 2017 Nov 7. doi: 10.1007/s12253-017-0354-8. [Epub ahead of print] No abstract available. PMID: 29116621(IF – 1.736)

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To the Editor,

Glioblastoma Multiforme (GBM) is a hot topic for research as the intimacies of this type of malignancy seem to be a long way from being truly understood. Diagnostically however, despite decades of research and many attempts at standardizing the histopathological diagnostic process, GBM remains an entity to be diagnosed by experienced neuropathologists.

3 F Kashlov JK, Donev IS, Doneva JG, Valkov VD, Kirkorova AD, Ghenev PI, Conev NV, Radeva TR, Ivanov BD, Georgieva ZT. Serum levels of RIPK3 and troponin I as potential biomarkers for predicting impaired left ventricular function in patients with myocardial infarction with ST segment elevation and normal troponin I levels prior percutaneous coronary intervention. *Biosci Trends* 2016;10(4):294-9. doi: 10.5582/bst.2016.01077. PMID: 27431004 Impact Factor 1.545

Summary

The current study examined the serum levels of receptor-interacting protein kinase 3 (RIPK3) in 51 patients with New York Heart Association (NYHA) class III-IV heart failure, 53 patients with myocardial infarction with ST elevation (STEMI), and 19 healthy subjects serving as a control group. An enzyme-linked immunoadsorbent assay (ELISA) was used to measure the levels of RIPK3 expression in serum. The area under the receiver operating characteristic curve (AUC) was then used to evaluate the predictive performance of RIPK3 and troponin I in patients with STEMI. In patients with normal levels of troponin I prior to percutaneous coronary intervention (PCI), serum levels of RIPK3 and troponin I after PCI were sufficient to differentiate patients with a preserved left ventricular ejection fraction (LVEF) from those with impaired left ventricular function after PCI (AUC = 0.780 (95% CI: 0.565-0.995, $p = 0.043$) with a sensitivity of 76.9% and a specificity of 71.4% vs. AUC = 0.735 (95% CI: 0.530-0.941, $p = 0.038$) with a sensitivity of 88.2% and a specificity of 63.6% at the optimal cutoff values, respectively). Moreover, elevated levels of troponin I after PCI were associated with an increased risk of an LVEF < 50% prior to discharge (odds ratio, 1.014; 95 % CI, 1.001 to 1.027; $p = 0.03$), while elevated levels of RIPK3 were not associated with such a risk. The current findings suggest that in patients with normal levels of troponin I prior to PCI, serum levels of RIPK3 and troponin I can serve as a potential marker to identify patients with a decreased LVEF, thus possibly allowing an early shift to more intensive therapy.

Keywords: Receptor-interacting protein kinase 3 (RIPK3), marker, percutaneous coronary intervention (PCI), left ventricular ejection fraction (LVEF)

4 F Chaldakov GN, Tunçel N, Beltowski J, Fiore M, Rancić G, Tonchev A, Panayotov P, Evtimov N, Hinev A, Anakievski D, Ghenev P, Aloe L. Adipoparacrinology: an emerging field in biomedical research. *Balkan Med J* 2012; 29: 2-9 • DOI: 10.5152/balkanmedj.2012.022

ABSTRACT

White adipose tissue (WAT) is a dynamic multicellular assembly composed of adipocytes and stromovascular cells, including fibroblasts, endothelial and immune cells, nerve fibers, and stem cells. In humans, WAT is a responsive and secretory (endocrine and paracrine) tissue partitioned into two large depots (subcutaneous and visceral) and many small depots associated with the heart, blood vessels, major lymph nodes, prostate gland, ovaries and mammary glands. This short review conceptualizes evidence for the paracrine activity of adipose tissue in founding a new research field, designated adipoparacrinology. Here we focus on (i) epicardial and periadventitial adipose tissue in atherogenesis, (ii) mammary gland-associated adipose tissue in breast cancer, and (iii) periprostatic adipose tissue in prostate cancer. Other examples include: (i) mesenteric adipose tissue in Crohn's disease, (ii) lymph node-associated (perinodal) adipose tissue in Crohn's disease and HIV-associated adipose redistribution syndrome, (iii) infrapatellar fat pad (Hoffa's fat pad) in knee osteoarthritis, (iv) orbital adipose tissue in thyroid-associated (Graves') ophthalmopathy, and (v) parasellar region-associated adipose tissue in brain disorders. The therapy aspect of adipoparacrinology is also discussed.

Key Words: Adipokines, atherosclerosis, breast cancer, epicardial adipose tissue, NGF, periadventitial adipose tissue, periprostatic adipose tissue, prostate cancer

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5 F Chaldakov GN, Beltowsky J, Ghenev PI, Fiore M, Panayotov P, Rancic G, Aloe L. Adipoparacrinology: vascular periadventitial adipose tissue (tunica adiposa) as an example. *Cell Biology International Immediate Publication*. 2012;36(3): 327-330 doi: 10.1042/CBI20110422
Published 12 Dec 2012, manuscript CBI20110422, Online publication date: 07 Feb 2012

Abstract

In humans, adipose tissue is partitioned into 2 large depots (subcutaneous and visceral), and many small depots associated with internal organs, e.g. heart, blood vessels, major lymph nodes, pancreas, prostate gland, ovaries. Since the Adipose's Big Bang was explored (Zhang et al., 1994), adipose tissue has been recognized as not merely lipid storage, but a secretory - endocrine and paracrine - organ, particularly in the pathogenesis of various diseases. Accordingly, 2 major sub-fields of adipobiology have emerged, adipoendocrinology and adipoparacrinology (Chaldakov et al., 2001), the latter is herein illustrated with the periadventitial adipose tissue

6 F Yamada T, Ohtsubo K, Izumi K, Takeuchi S, Mouri H, Yamashita K, Yasumoto K, Ghenev P, Kitagawa S, Yano S. Metastatic renal cell carcinoma complicated with diffuse alveolar hemorrhage: a rare adverse effect of sunitinib. *Int J Clin Oncol* 2010, DOI 10.1007/s10147-010-0104-3

Abstract

We report a 67-year-old man with metastatic papillary renal cell carcinoma in whom bloody sputum developed after administration of sunitinib. Chest computed tomography revealed diffuse ground-glass opacity lesions, and bloody bronchoalveolar lavage fluid was obtained by flexible bronchoscopy. The abnormal shadows promptly regressed after withdrawal of sunitinib. In four cycles of sunitinib treatment, he suffered from controllable diffuse alveolar hemorrhage. Finally, he died of respiratory failure eight months after onset.

7 F Chaldakov GN, Fiore M, Rančić G, Ghenev PI, Tuncel N, Beltowski J, Hristova MG, Atanassova P, Aloe L. Rethinking vascular wall: periadventitial adipose tissue (tunica adiposa). *Obesity and Metabolism* 2010; 6: 46-49

Abstract

[Edit](#)

The prevailing response-to-injury hypothesis of Russell Ross states that atherosclerosis is an inflammatory intimal disease. Accordingly, intima-media thickness became an accepted measure of structural arterial remodeling and a strong predictor of atherosclerosis. However, it is unlikely that such one-direction road may solely travel the whole multiplex network like that of atherogenesis. A decade ago, we have proposed an interactive hypothesis of atherogenesis, involving all structural components of the arterial wall including periadventitial adipose tissue (PAAT). As already alluded to, the arterial wall consists of three concentric tissue coats (tunicae): intima, media, and adventitia. In the present short review, we highlight accumulated data about PAAT, and conceptualize PAAT as the fourth coat of arterial wall, that is, tunica adiposa; in brief, adiposa, like intima, media, adventitia. Adiposa-derived adipokines - via paracrine way - may contribute to various vascular functions such as contraction-relaxation, smooth muscle cell growth, hemostasis, innervation, and inflammation. Altogether, the concept of tunica adiposa may contribute to further research in cardiovascular adipo-biology in health and disease.

8 F Hinev A, Klissarova A, Ghenev P, Kolev N, Chaushev B, Chankov P, Anakievski D, Dyakov S, Stratev S, Deliisky T. Radioisotopic detection of sentinel lymph nodes in clinically localized high-risk prostate cancer. *J BUON*. 2009 Oct-ec;14(4):661-7. PubMed PMID: 20148459.

Summary

Purpose: To explore the efficacy of a radioisotopic (RI) method in detecting sentinel lymph nodes (SLNs), known as sites of harboring metastases, in localized high-risk prostate cancer (HRPC).

Methods: The RI method was applied to 26 males with clinically localized HRPC, subjected to radical prostatectomy in 2006-2008. All had poor pathological characteristics: initial PSA > 15 ng/ml, Gleason score > 7, clinically suspected extracapsular extension, seminal vesicle invasion, and/or positive pelvic lymph nodes (LNs). The radiopharmaceutical (Tc-99m) was injected preoperatively at 4 zones of the periphery of the prostate. Tc-99m-nanocolloid particles were ≤ 80 nm in size, with total activity of 3 mCi (111 MBq), diluted in 2 mL. One hour after Tc-99m administration, a planar scintigraphy was performed on a gamma camera in anterior, posterior and lateral projections. A high resolution collimator was used, gathering impulses up to 300 000 per frame. The precise location of the SLNs was determined intraoperatively by a gamma probe. The LNs removed by extended pelvic lymphadenectomy were arranged on an anatomical template, examined *ex vivo*

by the gamma probe and scanned again. The LNs were cleaned from the adjacent fatty tissue, fixed in neutral formalin, and then processed separately for histological and immunohistochemical examination.

Results: The number of surgically removed LNs ranged from 9 to 38 (mean 13), and the SLNs from 1 to 7 (mean 3). The SLNs were visualized on lymphoscintigraphy as strictly defined, round zones of high activity and were easily recognized intraoperatively by the gamma probe. The scintigraphic images of the scanned anatomical templates correlated well with those prior to surgery. Histology confirmed LN metastases in 11 cases. 94% of the metastatic LNs were SLNs, accurately detected by the RI method. Only 2 metastatic LNs showed no activity prior to, and during the operation. Most of the metastatic LNs (62%) were SLNs, located out of the obturator fossa.

Conclusion: The radioisotopic detection of the SLNs in HRPC is an objective and sensitive method that aids the surgeon to take a proper decision regarding the scope of the pelvic LN dissection in each particular case.

Key words: gamma probe, lymph node dissection, lymphoscintigraphy, prostate cancer, sentinel lymph node

9 F Chaldakov G, Stankulov I, Hristova M, Ghenev P. Adipobiology of disease: Adipokines and adipokine-targeted pharmacology. *Curr Pharm Design* 2003;1023-1031

Abstract: In recent years, the simple paradigm of adipose tissue as merely a fat store is rapidly evolving into a complex paradigm of this tissue as multipotential secretory organ, partitioned into a few large depots, including visceral and subcutaneous location, and many small depots, associated with a variety of organs in the human body. The major secretory compartment of adipose tissue consists of adipocytes, fibroblasts, and mast cells. These cells, using endocrine, paracrine and autocrine pathways, secrete multiple bioactive molecules, conceptualized as adipokines or adipocytokines. This review examines current information in adipobiology of various diseases besides obesity and related diseases such as type 2 diabetes, metabolic syndrome, and cardiovascular disease. Finally, we emphasize the possibilities for adipokine-targeted pharmacology in adiponectin (Acrp30, apM1, AdipoQ, GBP28), angiotensin II, estrogens, nerve growth factor, tumor necrosis factor- α , and also adipose mast cells.



10 F Chaldakov GN, Stankulov IS, Fiore M, Ghenev PI, Aloe L. Nerve growth factor levels and mast cell distribution in human coronary atherosclerosis. *Atherosclerosis* 2001;159:57-66

Abstract

Nerve growth factor (NGF), in addition to its neurotrophic function, acts on a variety of non-neuronal cells including immune cells and vascular smooth muscle cells. The aim of the present study was to determine the NGF levels and the distribution of NGF and low-affinity NGF receptor (p75NGFR) and mast cells (MC) in human atherosclerotic coronary arteries. Specimens of human coronary arteries obtained from autopsy cases ($n = 12$, subjects with atherosclerotic lesions; $n = 9$, subjects without atherosclerotic lesions/controls) were used. The present study showed that in the atherosclerosis-lesioned arteries, the amount of NGF decreased, whereas the expression of p75NGFR immunoreactivity and the number, both of MC and vasa vasorum, particularly in the adventitia, significantly increased, compared with the control arteries. Cumulatively, our findings help to set the neurotrophic theory and its currently extended neuroimmune framework into the context of pathobiology of atherosclerosis, suggesting that altered presence of NGF, p75NGFR, and MC may play a role in neuroimmune mechanisms of human coronary atherosclerosis. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

11 L Chaldakov GN, Tonchev AB, Stankulov IS, Ghenev PI, Fiore M, Aloe L, Rančić G, Panayotov P, Kostov DD. Periadventitial adipose tissue (tunica adiposa): enemy or friend around? *Arch Pathol Lab Med.* 2007 Dec;131(12):1766; author reply 1766-7. No abstract available. PMID: 18081430

Periadventitial Adipose Tissue (Tunica Adiposa): Enemy or Friend Around?

To the Editor.—Recently, studies on the periadventitial adipose tissue (PAAT), a subfield of adipobiology, have attracted the attention of scientists because PAAT may indeed be a path to atherosclerosis.

In a recent issue of *Archives of Pathology & Laboratory Medicine*, Deborah Vela and colleagues¹ presented a review on the role of PAAT in atherosclerosis.

12 L Ghenev P, Chaldakov G. Adventitial heat shock protein 60 in human coronary atherosclerosis. *Atherosclerosis* 2004;172:189-190 (letter) molecules in health and disease. *Progress in Brain Research*. Elsevier, 2004;146; Chapter 18, 279-289

Adventitial heat shock protein 60 in human coronary atherosclerosis

Two recent papers in *Atherosclerosis* [1,2] updated the accumulating evidence for the atherogenic potential of heat shock proteins (HSP) in the molecular mimicry hypothesis of atherosclerosis [1–4]. In their review, Lamb et al. [1] also emphasized that “immunisation with HSP and HSP-containing vaccines exacerbates atherogenesis in experimental models.”

Here we provide further information regarding HSP significance in atherosclerosis. We studied the immunolocalization of HSP60 in specimens of human postmortem coronary arteries, using two primary monoclonal antibodies: LK1 (Sigma) and ML30 (gift from Jurai Ivanyi, Hammersmith Hospital, London, UK), and visualized them by streptavidin-biotin kit (DAKO) [5,6]. HSP60 was strongly expressed in atherosclerotic plaque area, while in normal coronaries and in lesion-free coronary circumference, very

13 L Ghenev PI, Chaldakov GN. Neural-immune links in adventitial remodeling in human coronary atherosclerosis (letter). *Circulation* 1997;96:2083-2084

Neural-Immune Links in Adventitial Remodeling in Human Coronary Atherosclerosis

To the Editor:

Shi et al¹ and Andersen et al² have described adventitial remodeling (neoadventitia) in coronary arterial injuries in pigs. However, data of such changes in human coronary atherosclerosis are few. We studied atherosclerotic coronary arteries from 63 autopsy cases (23 women and 40 men, 30 to 85 years of age), with the anterior descending branch of the left coronary artery being fixed in 10% formalin and processed for routine histochemistry. Corresponding to fibroatheroma, adventitial thickening, including either collagen fiber accumulation or mononuclear cell infiltration or both, was found. In 18 cases (28.6%), mononuclear infiltrations were established, half of which closely associated with perivascular nerve bundles. These

14 L Chaldakov GN, Valchanov K, Tonchev A, Ghenev PI. The association of mast cells and atherosclerosis: new insights into mast cells in atherogenesis. *Hum Pathol* 1995;26:1286

The Association of Mast Cells and Atherosclerosis: New Insights into Mast Cells in Atherogenesis

To the Editor:—Two recent papers^{1,2} provide further evidences for involvement of adventitial¹ and intimal² mast cells (MC) in atherogenesis. However, these authors' viewpoint of MC appears to be somehow "classical" thus missing some new concepts about these "master cells."³⁻⁵ In particular, we suggest that special attention should be focused not only on adventitial MC themselves,¹ but also on MC-nerve bidirectional links,³⁻⁵ also found in vascular adventitia,⁵ and MC as source of and target for a variety of cytokines, eg, tumor necrosis factor- α (TNF- α),³⁻⁵ nerve growth factor (NGF)^{4,5} and leukemia inhibitory factor.⁴ Note that a correlation between TNF- α and NGF levels and MC hyperplasia was shown to be

15 R K Ivanov, N Kolev, A Tonev, P Ghenev, N Zgurova, G Ivanov, T Kirilova, V Ignatov, A Zlatarov, A Tonchev. Expression of transcription factor Scratch2 in colorectal cancer. *J Clin Oncol* 2013; 31, (suppl; abstr e14669)

Abstract:

Background: The *Scratch* genes constitute an independent subgroup of the *Snail* superfamily of transcription factors (TFs). Vertebrates contain 2 *Snail* and 2 *Scratch* genes (*Sct1* and *Sct2*). Members of the *Snail/Scratch* superfamilies are characterized by a having both zinc finger domains, which mediate DNA-binding and a SNAG domain that is necessary for the transcriptional repression. Under normal conditions, the *Scratch* genes are expressed exclusively in the nervous system, where they regulate cortical neurogenesis (Paul, Tonchev, et al. *Cerebral Cortex* 2012, Epub ahead of print; doi: 10.1093/cercor/bhs356). However, expression of *Sct2* under pathological conditions is poorly characterized, especially in humans. **Methods:** We

16 R Ghenev P, Panayotov P, Chaldakov G, Aloe L. Periadventitial adipose tissue in human coronary atherosclerosis: a neurotrophin study. *Virchows Arch* 2012;461(Suppl.1):S259

PS-18-005

Periadventitial adipose tissue in human coronary atherosclerosis: A neurotrophin study

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Objective: Recent evidence demonstrates that epicardial adipose tissue, including coronary periadventitial adipose tissue (tunica adiposa), are paracrine sources of bioactive mediators (adipokines, NO, H₂S) which may be involved in coronary atherogenesis. Because of the increasing interest for extra-neuronal effects (inflammation, wound healing, lipid and glucose metabolism) of the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), including in human coronary atherosclerosis in autopsy samples, the aim of the present study is to evaluate the expression of NGF and BDNF and their receptors (TrkA and TrkB, respectively) in cardiosurgery biopsy samples of pericoronary adipose tissue.

17 R Hinev A, Klissarova A, Ghenev P, Kolev N, Chaushev B, Chankov P, Anakievski D, Dyakov S, Stratev S, Deliisky T. Radioisotopic detection of sentinel lymph nodes in clinically localized high-risk prostate cancer. *J BUON*. 2009 Oct-ec;14(4):661-7. PubMed PMID: 20148459.

RADIOISOTOPE DETECTION OF SENTINEL LYMPH NODES IN CLINICALLY LOCALIZED HIGH-RISK PROSTATE CANCER

Hinev A.I.¹, Klissarova A.D.², Ghenev P.I.³, Kolev N.H.⁴, Chaushev B.G.², Chankov P.K.¹, Anakievski D.¹, Dyakov S.¹, Stratev S.⁴, Deliisky T.S.⁵

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Introduction & Objectives: Although amenable to radical surgical excision, clinically localized high-risk prostate cancer (HR PC) is associated with a higher incidence of pelvic lymph node metastases. The aim of the present study was to explore the efficacy of the radioisotope method to detect the sentinel lymph nodes, known as the potential metastases harboring sites, in localized HR PC.

18 R Chaldakov GN, Tonchev AB, Stankulov IS, Ghenev PI, Fiore M, Aloe L, Rančić G, Panayotov P, Kostov DD. Periadventitial adipose tissue (tunica adiposa): enemy or friend around? *Arch Pathol Lab Med*. 2007 Dec;131(12):1766; author reply 1766-7. No abstract available. PMID: 18081430

PERIADVENTITIAL ADIPOSE TISSUE (TUNICA ADIPOSA): A FRIEND-AND-FOE CONCEPT OF ATHEROGENESIS

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The traditional thinking holds that (i) the vascular wall consists of tunica intima, t. media, and t. adventitia, and (ii) the intima is an "autonomic" territory of atherosclerosis, resulting from endothelial dysfunction and related inflammation. However, it might be more than that. A paradigm shift has emerged from recent studies in adipobiology, including (i) adipose tissue has both metabolic and secretory phenotype, and (ii) adipokines exert anti- and proinflammatory and vasorelaxing and contracting effects. We focus here on adventitia and periadventitial adipose tissue (PAAT) of human coronary arteries obtained from autopsies and during surgery.

19 R Ghenev P, Dandanov S, Dzhankov D, Kolova P. Comparative study of the morphological peculiarities of hormone-dependent breast cancer. *Virchows Arch* 2007;451:489, PP2-17

PP2-17

COMPARATIVE STUDY OF THE MORPHOLOGICAL PECULIARITIES OF HORMONE-DEPENDENT BREAST CANCER

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In defining the prognosis and the treatment strategies of breast cancers a constantly increasing number of morphological criteria are applied, such as more accurate gross characteristics, histological features, hormonal status of cancers cells, and the involvement of axillary lymph nodes. The aim of the present study is to assess the morphological peculiarities and the immunohistochemical profile of estrogen, progesterone and HER2 receptor positive tumors. These findings were correlated with patient and tumor characteristics at the time of surgery. In

20 R Ghenev PI, Stankulov IS, Tonchev AB, Chaldakov GN. Immunohistochemical study of the adipose tissue in a fatal case of arrhythmogenic right ventricular dysplasia. *Virchows Arch* 2007;451:489, PP3-320

PP3-320

IMUNOHISTOCHEMICAL STUDY OF THE ADIPOSE TISSUE IN A FATAL CASE OF ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

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Arrhythmogenic right ventricular dysplasia (ARVD) is a heritable disorder characterized by progressive degeneration and fibro-fatty replacement of right ventricular myocardium, causing ventricular tachyarrhythmias and resulting in sudden death at a young age. We report a young man without prior complaints dying suddenly during minor physical effort. The gross autopsy findings in the heart were minimal. The histologic features in both right and left ventricles were typical of ARVD, and consisted of fatty infiltrates with typical cardiomyocyte degeneration of the right ventricle and subepicardial regions of the left ventricle. Several lines of evidence suggest that

21 R G.N.Chaldakov, I.S.Stankulov, P.Atanassova, M.Fiore, P.I.Ghenev, A.B.Tonchev, L.Aloe
Adipobiology of Atherosclerosis XIV International Symposium on Atherosclerosis, Rome, Italy,
June 18-22, 2006

Tu-P7:16 ADIPOBIOLOGY OF ATHEROSCLEROSIS

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Objective: Adipose tissue is not solely a fat storage, but an active endocrine and paracrine organ secreting a variety of molecules conceptually dubbed adipokines. The present study aimed at evaluating the role of epicardial adipose tissue in the pathogenesis of human coronary atherosclerosis.

22 R P. Ghenev, I. Stankulov, A. Tonchev, G. Chaldakov. Atherosclerotic changes in human coronary arteries: adventitia - the other side of the coin. *Atherosclerosis Suppl* 2004; 5(1):6, Proc. 74th EAS Congress, 17-20 April 2004, Seville, Spain. WO1.25

W01.25

ATHEROSCLEROTIC CHANGES IN HUMAN CORONARY ARTERIES: ADVENTITIA – THE OTHER SIDE OF THE COIN

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Russell Ross' response-to-injury paradigm, considers atherosclerosis as "a protective, inflammatory-fibroproliferative response" to harmful stimuli, resulting in intimal lesions. That is why most of the research work is concentrated upon intima, while adventitia, i.e. "the other side of the coin" is neglected. Several lines of evidence (Booth et al 1989, Martin et al 1990, Yong et al 1992, Wilcox, Scott 1996, Kwon et al 1998, Yutani et al 1999) clearly show that adventitia/adventitial cellular components are not innocent bystanders in atherogenesis. On the other hand, data accumulate about the role of heat shock proteins 60 (HSP60) in atherosclerotic lesions initiation (Xu et al 1992, Kol et al 1998, Wick 2000, Mayr et al 2000, Zhu et al 2001). The aim of the present study is to evaluate quantitatively the adventitial changes and the immunohistochemical expression of (HSP60) in postmortem human atherosclerotic coronary arteries. The cellular com-

23 R Chaldakov G, Fiore M, Stankulov I, Manni L, Hristova MG, Antonelli A, Ghenev P, Aloe L. Metabotropic deficit hypothesis: Reduced levels of the neurotrophins NGF and BDNF in atherosclerosis and metabolic syndrome. *Atherosclerosis* 2003;4:46,1P-0120

Abstract

In addition to their stimulatory action on neuronal differentiation and survival, the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) improve glucose and lipid metabolism and control energy balance and feeding behavior. These latter activities are referred to here as the metabotropic potential of neurotrophins. We recently reported that circulating NGF and BDNF levels are reduced in the metabolic syndrome and in acute coronary syndromes, and that the tissue content of NGF is reduced in atherosclerotic coronary arteries. Thus we hypothesize that a metabotropic deficit due to reduction of neurotrophin availability may be implicated in the pathogenesis of obesity and related metabolic diseases, such as metabolic syndrome, type 2 diabetes, and atherosclerosis. The metabotropic deficit hypothesis also considers metabolism-related beneficial effects exerted by other neurotrophic factors, particularly ciliary neurotrophic factor, leukemia inhibitory factor, and bone morphogenetic proteins.

24 R Manevska B, Dokov V, Ghenev P, Dokov W. Nonsymptomatic nontumor cysts of the pineal gland: frequency and morphological characteristics. *Virch Arch* 2003;443:P-230

P-230

Nonsymptomatic nontumor cysts of the pineal gland: frequency and morphological characteristics

B Manevska, V Dokov, P Ghenev, W Dokov
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Introduction Nonsymptomatic nontumor cysts (NNC) of the pineal gland (PG) are considered as normal structures. The aim of the present study is to evaluate the frequency of NNC in random postmortem examinations and their influence upon surrounding parenchyma.

25 R Manevska B, Ghenev P, Stankulov I, Tonchev A, Chaldakov G. Morphometric analysis of atherosclerotic changes in the adventitia of human coronary arteries. *Virch Arch* 2003;443:P-527

P-527

Morphometric analysis of atherosclerotic changes in human coronary arteries adventitia

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Medical University of Varna, Varna, Bulgaria

Introduction Nowadays understanding of atherogenesis, Russell Ross' response-to-injury paradigm, considers atherosclerotic lesions as "a protective, inflammatory-fibroproliferative response" to harmful stimuli. Among these stimuli are the major risk factors, which contribute for atherosclerotic cardiovascular complications. Arterial blood flow impairment is associated with the progression of intimal atherosclerotic lesions. That is why most of the research work is concentrated upon intima, while adventitia is neglected. Several lines of evidence clearly show that adventitia is not an innocent bystander in atherogenesis. The aim of the present study is to evaluate morphologically adventitial changes in atherosclerotic arteries.

26 R Chaldakov G, Properzi F, Ghenev P, Fiore M, Stankulov I, Aloe L. Artery-associated adipose tissue and atherosclerosis: a correlative study of NGF, p75NGF receptor and mast cells in human coronary atherosclerosis. *Atherosclerosis* 1999;146 Suppl I:S33

56

ARTERY-ASSOCIATED ADIPOSE TISSUE AND
ATHEROSCLEROSIS: A CORRELATIVE STUDY OF NGF,
p75NGF RECEPTOR AND MAST CELLS IN HUMAN CORO-
NARY ATHEROSCLEROSIS

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Alterations of lipid metabolism are "classically" implicated in the pathobiology of atherosclerosis, an inflammatory fibroproliferative disease. Recent evidence indicates that adventitial manipulation of the vessel induces intimal hyperplastic lesions, thus suggesting that the outer arterial layers are involved in atherogenesis. Therefore, it seems reasonable to suspect that investigating periadventitial tissue, i.e. the adipose tissue, could prove to be potentially useful in further understanding of the atherosclerotic process. We previously demonstrated that the NGF level was significantly lower, the immunostaining for p75NGF receptor (p75NGFR) was more intense, and the number of MC/vasa vasorum was greater in human atherosclerotic versus nonatherosclerotic coronary arteries. Here we present the first evidence suggesting that the adipose tissue associated with the artery wall is not an innocent bystander, but probably a paracrine, adipose tissue-to-adventitia participant in the development of atherosclerosis.

27 R Manevska B, Ghenev P. Mesenchymal (stromal) tumors of the gastrointestinal tract; endoscopic biopsy diagnostic, morphological and immunohistochemical characteristics. *Virchows Archiv* 1999;35:352A

P-639

MESENCHYMAL (STROMAL) TUMORS OF THE GASTROINTESTINAL TRACT: ENDOSCOPIC BIOPSY DIAGNOSTIC, MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL CHARACTERISTICS

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Aims: To study the incidence and peculiarities of gastrointestinal tract (GIT) mesenchymal tumors in order to estimate the diagnostic obstacles and their morphogenesis.

Methods: Fifteen GIT mesenchymal tumors from endoscopic biopsies and subsequent resection materials were analyzed. Paraffin sections were stained after HE, Mallory and Gomori. Immunohistochemical procedures were performed using primary antibodies against vimentin, cytokeratin, desmin, S-100 protein and LSAB kit (all from DAKO).

28 R Valchanov K, Tonchev A, Pancheva R, Andonov M, Ghenev P, Chaldakov G. Cardiac mast cell proliferation: response to estradiol treatment of neonatal rats. XII Natl Congress Bulgarian Anatomical Society, *Eur J Morphol* 1997;35:65 (abstract)

CARDIAC MAST CELL PROLIFERATION: RESPONSE TO ESTRADIOL TREATMENT OF NEONATAL RATS

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Mast cells are supposed to be regulated via estradiol influence on testicular cells, especially Leydig and Sertoli cells. Newborn male rats were examined for the influence of estradiol on mast cells in both heart and testis. For comparison, the already studied paradigm of Gaytan et al. (1990) for the testicular interstitium was used.

Пълнотекстови научни публикации:

1 FT Chaldakov GN, Fiore M, Ghenev PI, Stankulov IS, Angelucci F, Pavlov PS, Aloe L. Conceptual novelties in atherogenesis: Smooth muscle cells, adventitia and adipose tissue. *Biomed Rev* 2000;11:63-67

Here the questions we are dancing round include conceptually new findings about the role of arterial smooth muscle cells (SMC), adventitia, and adipose tissue, particularly, artery-associated adipose tissue (AAAT) in the formation and dynamics of atherosclerotic lesions.

THE SMOOTH MUSCLE CELL: OCCLUSION VERSUS RUPTURE

2 FT Chaldakov GN, Stankulov IS, Fiore M, Hristova M, Rancic G, Ghenev PI, Pavlov P. Adipoendocrinology and adipoparacrinology: emerging fields of study on the adipose tissue. *Biomed Rev* 2001;12:31-40

Adipose tissue was conceived originally as merely passive, space-filling, fat storage tissue. However, in the last 10 years, investigations aimed at studying the endocrine secretion by adipose tissue have enjoyed explosive growth. The major secretory compartment of adipose tissue consists of adipocytes and stromal fibroblasts (adipofibroblasts). These cells secrete multiple bioactive molecules, conceptualized as adipokines or adipocytokines. Overall, this intellectual growth process framed an emerging field of study, adipoendocrinology. "Adipoendocrinology" connotes the study of the cellular and molecular biology of the endocrine function of adipose tissue in normal and diseased conditions. In humans, white adipose tissue is partitioned into a few large depots, including visceral and subcutaneous location, and many small depots, associated with heart, large blood vessels, major lymph nodes and other organs. The possibility that the endocrine secretory activity of large adipose depots may directly contribute to the elevated plasma levels of disease-associated adipokines has recently gained considerable attention. However, the paracrine secretory activity of organ-associated adipose tissue (the small adipose depots) has until now attracted little attention in the adipobiology of disease. Here we attempt to emphasize that studies aimed at evaluation of the paracrine secretion of organ-associated adipose tissue are becoming mandatory, since identification of the secreted molecules, particularly, adipokines, may yield clues to a possible transmission of pathogenic and or protective stimuli, from the associated adipose tissue towards the interior of the associating organ. In this review we summarize most of the current information about adipoendocrinology and adipoparacrinology of various diseases.

Biomed Rev 2001; 12: 31-39.

3 FT Ignatov V, P. Ghenev, E. Kiryazov, N. Kolev. Morphological changes in the tissues under the action of ND:YAG laser in peptic ulcer bleeding. *Scripta Scientifica Medica*, 2004; 36: 51-5

ABSTRACT

The authors carry out a morphological study of 60 endoscopic biopsies of stomach mucosa followed-up consequentially in time. The study describes the morphological changes in the tissues under the action of Nd:YAG laser beam in cases of acute bleeding from peptic ulcers. Study proves that Nd:YAG LFC has lasting haemostatic and epithelising effect, i. e. it exerts a long-lasting therapeutic effect.

Key words: bleeding, haemostatic and epithelising effect, gastroduodenal ulcer, histomorphology

4 FT Tonchev AB, Stankulov IS, Ghenev PI, Pavlov PS, Chaldakov GN, Yamashima T. Identification of putative progenitor cells in the anterior subventricular zone of the adult human brain. *C R Bulg Acad Sci* 2006; 59; 683-686.

Abstract

The subventricular zone along the anterior horn (SVZa) of the lateral ventricle in the brain contains progenitor cells which are capable of neuronal generation in adulthood in a process referred to as adult neurogenesis. Despite the significant recent progress in deciphering the molecular mechanisms controlling SVZa progenitors in rodents, little is known of these mechanisms in primate's brain. The early precursor marker A2B5 has been useful in the *in vitro* isolation of progenitor cells from adult human parenchyma, but whether this antigen is localized on cells in human SVZa and what could be their phenotype remains elusive. We identified A2B5 in SVZa of brain samples derived from adult humans. A2B5-positive cells co-localized with the proliferation marker Ki67 and with the progenitor cell marker vimentin, and exhibited mitotic figures. These results suggest that A2B5 is expressed by progenitor cells of adult human SVZa.

Key words: A2B5, vimentin, cell proliferation, primate

5 FT Chaldakov G, Fiore M, Stankulov I, Manni L, Hristova MG, Antonelli A, Ghenev P, Aloe L. Neurotrophin presence in human coronary atherosclerosis and metabolic syndrome: a role for NGF and BDNF in cardiovascular disease? In: Aloe L, Calza L, editors. *NGF and related molecules in health and disease. Progress in Brain Research.* Elsevier, 2004;146; Chapter 18, 279-289

Abstract: The development of atherosclerotic cardiovascular disease is a common comorbidity in patients with the metabolic syndrome, a concurrence of cardiovascular risk factors in one individual. While multiple growth factors and adipokines are identified in atherosclerotic lesions, as well as neurotrophins implicated in both cardiac ischemia and lipid and glucose metabolism, the potential role of neurotrophins in human coronary atherosclerosis and in the metabolic syndrome still remains to be elucidated. Here we describe and discuss our results that represent a novel attempt to study the cardiovascular and metabolic biology of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and mast cells (MC). The local amount of NGF, the immunolocalization of p75 neurotrophin receptor (p75^{NTR}) and the number of MC were correlatively examined in coronary vascular wall and in the surrounding subepicardial adipose tissue, obtained from autopsy cases in humans with advanced coronary atherosclerosis. We also analyzed the plasma levels of NGF, BDNF and leptin and the number of MC in biopsies from abdominal subcutaneous adipose tissue in patients with a severe form of the metabolic syndrome. The results demonstrate that NGF levels are decreased in atherosclerotic coronary vascular tissue but increased in the subepicardial adipose tissue, whereas both tissues express a greater number of MC and a stronger p75^{NTR} immunoreactivity, compared to controls. Metabolic syndrome patients display a significant hyponeurotrophinemia and an increased number of adipose MC; the later correlates with elevated plasma leptin levels. In effect, we provide the first evidence for (i) an altered presence of NGF, p75^{NTR} and MC in both coronary vascular and subepicardial adipose tissue in human coronary atherosclerosis, and (ii) a significant decrease in plasma NGF and BDNF levels and an elevated amount of plasma leptin and adipose MC in metabolic syndrome patients. Together our findings suggest that neuroimmune mediators such as NGF, BDNF, leptin and MC may be involved in the development of cardiovascular disease and related disorders.

6 FT Chaldakov GN, Tonchev AB, Georgieva G, Ghenev PI, Stankulov IS. Adipobiology of inflammation. *Biomed Rev* 2005; 16: 83-88.

*Besides its importance for glucose, lipid and energy metabolism, the present paradigm defines adipose tissue as the body's largest endocrine and paracrine organ. Accumulating evidence demonstrates that adipose tissue cells synthesize and release a large number of signaling proteins collectively termed adipokines. Adipokines regulate a broad spectrum of biological processes, with inflammation being a key example. This defines a new field of study: adipobiology of inflammation. Here we shall dance round it, supposing that the pathogenesis of inflammation-related diseases such as atherosclerosis, thyroid-associated ophthalmopathy, inflammatory bowel diseases, and breast cancer may be influenced by competing stimulatory and inhibitory effects mediated by adipokines. This concept may reveal new tools for the development of adipopharmacology of inflammatory disease. **Biomed Rev 2005; 16: 83-88.***

Key words: adipokines, adipose tissue, atherosclerosis, breast cancer, Crohn's disease, ophthalmopathy

7 FT N.Peev, S.K.Kalevski, D.G.Haritonov, P.I.Ghenev, I.J.Karasnaliev, Isolated Rosai-Dorfman Disease of the Cerebellar Hemisphere as a Rare Differential Diagnosis of Metastatic Brain Disease. Case Report. Nepal Journal of Neuroscience, 2008

Sinus Histiocytosis with Massive Lymphadenopathy, or Rosai-Dorfman disease (RDD), is a rare histiocytic proliferative disorder. Generally patients present with massive cervical lymphadenopathy. Intracranial localization is a rare manifestation of RDD. The majority of the cases with intracranial involvement are reported to be with supratentorial, dural-based localization. Only a few cases of the posterior cranial fossa involvement have been reported in the literature. We report a case of isolated cerebellar hemisphere RDD which was initially misdiagnosed as a metastatic brain disease.

Key words: cerebellar, brain, metastases, isolated, Rosai-Dorfman,

8 FT Dimitrov D, Pancheva R, Tonchev AB, Stoeva K, Kostov D, Georgieva Z, Ghenev PI, Chaldakov GN. Nutrigenomics: DNA-based individualized nutrition. Biomed Rev 2006;17:119-124

*In the past decade, nutrition research has undergone an important shift from epidemiology and physiology to molecular biology, adipobiology and genetics, thus launching the science of nutrigenomics. To at molecular level study effects of nutrition on health and disease. The completion of several large genome projects has markedly altered the research agenda by drawing attention to the importance of genes in human nutrition. There has been a growing recognition that micronutrients and macronutrients can be potent dietary signals that influence the metabolic pathways of cells and have an important role in the control of energy, vascular and neuronal homeostasis. Accordingly, nutrition researchers have increasingly started to recognize that gene-environment interactions can be implicated in the pathogenesis of lifestyle-related diseases, particularly cardiometabolic diseases, fatty liver diseases, cancers, and Alzheimer's disease. An adiponutrigenomic insight into life expectancy is also outlined. Overall, the present Dance Round focuses on a matter of nationwide importance for Bulgaria, a country at the epicenter of today's global healthquake, the obesity and related diseases. **Biomed Rev 2006; 17: 117-122.***

9 FT Chaldakov GN, Fiore M, Ghenev PI, Sornelli F, Tonchev AB, Aloe L. Neural-immune-endocrine (NIE) interactions in vascular biology: Neurotrophins, immune cells, and tunica adiposa. In: Gianluca Iacobellis, editor; J Endocardiol 2008;1 Issue 2: 73-84 Nova Science Publishers, Inc

ABSTRACT

It was recently postulated that the periadventitial adipose tissue composes the vascular wall's fourth, outermost coat designated *tunica adiposa*. An artery affected by atherosclerosis displays intimal thickening, medial atrophy and adventitial lesions associated with adipose dysfunction. Although "many roads lead to atheroma", the prevailing hypothesis at present is the Russell Ross' response-to-injury hypothesis, which states that atherosclerosis is an inflammatory disease that involves several aspects of wound healing. However, the role of the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) and their functional integration with immune cells and endocrine adipose tissue has been recently emerged. Here we highlight the possibility that neural-immune-endocrine (NIE) interactions operating at *tunica adventitia* and *tunica adiposa* may play an important role in the pathogenesis of atherosclerosis. Accordingly, NIE-targeted pharmacology may provide a novel preventive and therapeutic approach in vascular biology.

10 FT Chaldakov GN, Fiore M, Rančić G, Tonchev AB, Hristova MG, Tunçel N, Kostov DD, Bojanić V, Atanassova P, Ghenev PI, Aloe L The adipose tissue: a new member of the diffuse neuroendocrine system? Adipobiology 2009;1:87

Abstract

Adipose tissue is a sophisticated module, consisting of adipocytes and non-adipocyte cellular elements including stromal, vascular, nerve and immune cells. There is at present evidence that sharing of ligands and their receptors constitutes a molecular language of the human's body, which is also the case for adipose tissue and hypothalamus-pituitary gland. Historically, Nikolai Kulchitsky's identification of the enterochromaffin cell in 1897 formed the basis for the subsequent delineation of the diffuse neuroendocrine system (DNES) by Friedrich Feyrter in 1938. In DNES paradigm, the secretion of hormones, neuropeptides and neurotrophic factors is executed by cells disseminated throughout the body, for example, Kulchitsky (enterochromaffin) cells, testicular Leydig cells, and hepatic stellate cells. Here we propose that the adipose tissue might be a new member of DNES. Today (*dnes*, in Bulgarian), adipose tissue is "getting nervous" indeed: (i) synthesizes neuropeptides, neurotrophic factors, neurotransmitters, hypothalamic hormones/releasing factors and their receptors, (ii) like brain expresses endocannabinoids and amyloid precursor protein and, for steroidogenesis, the enzyme aromatase (P450arom), (iii) adipocytes may originate from the neural crest cells, and (iv) adipose-derived stem cells may differentiate into neuronal cells. Further molecular profiling of adipose tissue may provide new biological insights on its neuroendocrine potential. Overall this may frame a novel field of study, neuroadipobiology; its development and clinical application may contribute to the improvement of human's health.

Adipobiology 2009; 1:87-93

11 FT Chaldakov GN, Fiore M, Ghenev PI, Tunçel N, Rančić G, Atanassova P, Aloe L. State-of-the-artery: periadventitial adipose tissue (tunica adiposa). *Biomed Rev* 2009;20:41-45

INTRODUCTION

In 1983 at Department of Anatomy, University of Chicago Medical School, Chicago, IL, USA, one of us (GNC) delivered a lecture about fibroblast-like secretion by vascular smooth muscle cells, a key cell type in atherogenesis. During the discussion, a question whether adventitial fibroblasts may migrate into the intima was raised. The answer of the lecturer was “I do not know. It seems impossible”. However, what seemed “impossible” in 1983 was proven possible in 1996 by Shi et al (1).

12 FT Chaldakov GN, Aloe L, Hristova MG, Tonchev AB, Nikolova V, Panayotov P, Ghenev PI. NGF-ome: its metabotropic expression. Homage to Rita Levi-Montalcini. *Biomed Rev* 2010; 21: 25-29.

*Nowadays, in the postgenome time, many “-ome” studies have emerged including proteome, transcriptome, interactome, metabolome, adipokinome, connectome. In this vein, the catchall term NGF-ome embodies all the actions of NGF in health and disease. Accordingly, the present Festschrift, also tabula gratulatoria, is to honor and acknowledge the contributions of the distinguished neuroscientist and magistra Rita Levi-Montalcini, the Nobel Prize winner-1986 for the discoverer of NGF. Today, NGF and another neurotrophin, brain-derived neurotrophic factor (BDNF), are well recognized to mediate multiple biological phenomena, ranging from the neurotrophic through immunotrophic and epitheliotrophic to metabotropic effects. These latter effects are involved in the maintenance of cardiometabolic homeostasis (glucose and lipid metabolism as well as energy balance, and cardioprotection). Circulating and/or tissue levels of NGF and BDNF are altered in cardiometabolic diseases (atherosclerosis, obesity, type 2 diabetes, metabolic syndrome, and type 3 diabetes/Alzheimer’s disease). A hypothesis thus emerged that a metabotropic deficit due to the reduction of NGF/BDNF availability and/or utilization may be implicated in the pathogenesis of cardiometabolic and neurodegenerative diseases. The present challenge is therefore to cultivate a metabotropic thinking about how we can modulate NGF/BDNF secretion and signaling for the benefit of human cardiometabolic and mood health. **Biomed Rev** 2010; 21: 25-29.*

13 FT Tonchev AB, Aloe A, Beltowski J, Rančić G, Bojanić V, Atanassova P, Ghenev PI, Chaldakov GN. Adipose-derived stem cells as a remedy. *Adipobiology* 2010; 2:51-56

Abstract

Adipobiology of stem cells is reaching enthusiastic proportions in today’s regenerative medicine. Current interest in the adipose-derived stem cells (ADSC) stems from their multilineage differentiation potential, and ease of derivation in larger quantities using less invasive methods, compared with other stem cell types. The possible benefits of ADSC-based therapy may be mediated by both cell proliferation/differentiation and paracrine secretion. Adipose tissue’s secretome includes adipokines (growth factors, cytokines, chemokines, neuropeptides, hypothalamic hormones/releasing factors), steroid hormones, free fatty acids, prostaglandins, and endocannabinoids. The present review, focusing on adipose tissue secretory activity, also highlights the possible implication of ADSC in the therapy of various disorders, particularly neurodegenerative diseases, myocardial infarction and stroke as well as gut, liver and skin diseases.

Adipobiology 2010; 2:51-56

14 FT Ghenev P, Stankulov I, Dokov V, Dokow W. Arrhythmogenic right ventricular dysplasia – analysis of three fatal cases. Acta morphol anthropol 2010;15:150-154

Introduction

Arrhythmogenic right ventricular dysplasia (ARVD), or cardiomyopathy (ARVC) is an underrecognized clinical entity, with unknown cause and prevalence and with a frequent familial occurrence (1, 2). Morphologically, it is characterized by progressive degeneration of cardiomyocytes and fibro-fatty replacement of right ventricular myocardium, causing electrical instability, ventricular tachyarrhythmias with left bundle branch block and sudden death at a young age (3, 4, 5). ARVD is a rare disorder, but for a short period of time, three cases were proven by forensic pathology autopsies in a relatively small region in the northeastern part of Bulgaria.

The aim of the present study is to analyze the autopsy findings in these cases.

15 FT Evtimov N, Hinev AI, Anakievski D, Zhelezov M, Ghenev PI, Chalakov GN. Adipoparacrinology: periprostatic adipose tissue as an example. Adipobiology 2011;3:61-65

Abstract

The global epidemic of obesity (globesity) and related cardiometabolic and cancer diseases has focused attention on adipose tissue biology and the role played by adipose-secreted bioactive molecules (adipokines, neurotrophic factors, fatty acids, prostaglandins, steroid hormones, vitamin D3, NO, H2S) in the regulation of a wide array of physiological and pathological processes. Until recently, physicians have looked upon obesity as an accumulation of external adipose tissue (subcutaneous and abdominal). This was routinely evaluated by anthropometric measurements including body mass index and waist, hip and, recently, neck circumference. However, recent data using non-invasive imaging methods (echography, computed tomography, magnetic resonance imaging, and positron emission tomography), reveal a novel picture of adipotopography (fat mapping). Together with secretory functions, such a topography has been conceptualized as two major subfields of adipobiology, adipoendocrinology and adipoparacrinology. Here we introduce periprostatic adipose tissue as an example of adipoparacrinology of prostate cancer; its implication in the therapy is also outlined.

Adipobiology 2011; 3: 61-65

16 FT Н Цонев, И Донев, Т Червенков, А Консулова, П Ганев, Е Димитрова, Д Калев. Влияние на Микрорибонуклеинови киселини върху сигнални клетъчни пътища при колоректален карцином. Списание на Българското Онкологично Дружество 2012;1: 44-48
ISSN 1312-6601

РЕЗЮМЕ

Сигналният път на фосфатидил-инозитол 3-киназите (PI3K)/Akt има важно влияние върху неопластичния растеж, оцеляване, мотилитет, метаболизъм и е най-често активираната каскада при човешки тумори. Синтезирани са много PI3K-инхибитори, които навлизат в клинични изпитвания.

Цел на този обзор е да дискутира ролята на PI3Ks в туморогенезата и данните, подкрепящи използването на PI3K-инхибитори в клиничната практика.

КЛЮЧОВИ ДУМИ

PI3K/Akt сигнален път, PI3K-инхибитори

17 FT Popov. H, Ghenev P. Comparative analysis of relapsing bladder urothelial cancer. Acta morphologica et anthropologica. 2012; 192-195.

Introduction

Tumors of bladder consist of 90-95% of all neoplasms in the urogenital system. Their frequency is 12,4:100 000 people (1).

Bladder cancer represents a problem in the clinical practice with the high percentage of relapsing, even in high-grade cancer. At microscopic level, there are no convincing objective criteria for evaluation of the tendency for local relapsing, invasion in the wall and/or metastases. In this regard, possible signs could be derived from the peculiarities of the stroma, such as presence of eosinophil leukocytes, mast cells, lymphocytes, plasmocytes, fibroblast and myoepithelial cells. Increased numbers of eosinophil leukocytes is described in many malignant tumors and their presence is considered either with good or poor prognosis in the different cancer locations. The exact role of these cells in the anti-tumor immunity is not clear. Their activity is connected with: secretion of cytotoxic proteins (2); and basal membrane damage by eosinophil-derived cation proteins and peroxidase (3). Thus, products released by eosinophils interfere in the majority of processes of tissue remodeling, including the biological behaviour of tumors (4).

18 FT Г.Чалдъков, П.Генев, К.Костов Бронхиално и васкуларно възпаление: две локализации – един механизъм. In Spigo бр.2 юни 2012

Известно е, че хронична обструктивна белодробна болест (ХОББ), бронхиална астма и атеросклероза са хронични възпалителни (*low grade inflammatory*) болести¹⁻⁸. Ние представяме концептуална хипотеза, наречена „*две локализации-един механизъм*“. Тази хипотеза постулира, че перибронхиално (в адвенцицията) и периваскуларно (в адвенцицията и периадвенцициалната мастна тъкан/*tunica adiposa*) действа принципно един и същ клетъчно-молекулен механизъм: *възпаление-ремоделиране-фиброза*. Това води до оклузия на бронхиоли и артерии, причинявайки съответно задух (ХОББ и астма), *ангина пекторис* (коронарна атеросклероза) и *клаудикацио интермитенс* (периферна атеросклероза).

19 FT И. Бакърджиев, Т. Драгнева, Г. Пехливанов, Г. Чернев, М. Гоневски, П. Генов. Базоцелуларен карцином с аксиларна локализация - рядък случай от клиничната практика. Дерматологичен преглед 2012; 1 (1): 22-25

Резюме

Базоцелуларният карцином (BCC) е една от най-честите неоплазми в човешката патология, която представлява около 75 % от всички немеланомни тумори на кожата. Аксиларната област е добре защитена от слънчева експозиция и локализацията на базоцелуларния карцином в тази област е относително рядка. Само 34 случая на аксиларен BCC са описани в световната литература. Представя се 72 годишна жена, при която оплакванията датират от около 5 години, когато в дясната аксиларна област се появило образувание, което постепенно увеличило размерите си. Фамилно необременена. Минали заболявания отрича. В рамките на дерматологичния преглед бе установена улцерирана асиметрична плака с приблизителни размери около 13 мм и добре изразени перлообразни граници, леко болезнена при палпация. Аксиларно локализираните лимфни възли- неувеличени. Извършена е елиптична екцизия с последващо хистопатологична верификация, която показа: кожа с изтъняване на дермата и солидни гнезда от мономорфни туморни клетки с палисадно подреждане в периферията. Рецидив на тумора не беше открит в хода на 24 месечното клинично проследяване

Ключови думи: базоцелуларен карцином, аксиларна област, елиптична екцизия

20 FT I. Dimitrov, T. Avramov, A. Kaprelyan, R. Georgiev, Y. Entchev, B. Ivanov, P. Genev, I. Krasnaliev, N. Deleva [A rare case of hypertrophic spinal luetic meningitis presenting as a transverse lesion of the spinal cord. Bulg Neurol 2013. 12/2013; 14\(3\):162- 167.](#)

SUMMARY

Neurosyphilis has various clinical presentations. It is relatively rare in neurological practice, but remains a significant diagnostic and therapeutic challenge. In the present article we present a clinical case of hypertrophic spinal syphilitic meningitis, presenting as a transverse lesion of the spinal cord at the thoracic level, with spastic paraparesis, sensory loss, and urinary retention, as a result of subacute cord compression in a patient with previously unidentified syphilis. We discuss the diagnostic difficulties in similar cases, caused by the broad spectrum of possible differential diagnoses, as well as by the insufficient informative value of standard assessments. Images from magnetic resonance tomography and from the histological assessment of biopsy material are included. We underline the importance of early diagnosis which determines to a large extent the therapeutic results and the outcome of the disease. We emphasize the importance of neurosurgery, not only in the therapeutic but also in the diagnostic process. This clinical case suggests the usefulness of a wider application of *Treponema pallidum* infection screening in neurological practice.

KEYWORDS: Neurosyphilis, neuroinfection, hypertrophic meningitis, spinal cord compression

21 FT GN Chalidakov, M Fiore, PI Ghenev, J Beltowski, G Rancic, N Tunçel, L Aloe. Triactome: neuro-immune-adipose interactions. Implication in vascular biology. *Frontiers in Immunology | Inflammation* 2014;5:130 Article130 doi: 10.3389/fimmu.2014.00130 PMID: PMC3986561

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Understanding how the precise interactions of nerves, immune cells, and adipose tissue account for cardiovascular and metabolic biology is a central aim of biomedical research at present. A long standing paradigm holds that the vascular wall is composed of three concentric tissue coats (*tunicae*): intima, media, and adventitia. However, large- and medium-sized arteries, where usually atherosclerotic lesions develop, are consistently surrounded by periadventitial adipose tissue (PAAT), we recently designated *tunica adiposa* (in brief, adiposa like intima, media, and adventitia). Today, atherosclerosis is considered an immune-mediated inflammatory disease featured by endothelial dysfunction/intimal thickening, medial atrophy, and adventitial lesions associated with adipose dysfunction, whereas hypertension is characterized by hyperinnervation-associated medial thickening due to smooth muscle cell hypertrophy/hyperplasia. PAAT expansion is associated with increased infiltration of immune cells, both adipocytes and immunocytes secreting pro-inflammatory and anti-inflammatory (metabotropic) signaling proteins collectively dubbed adipokines. However, the role of vascular nerves and their interactions with immune cells and paracrine adipose tissue is not yet evaluated in such an integrated way. The present review attempts to briefly highlight the findings in basic and translational sciences in this area focusing on neuro-immune-adipose interactions, herein referred to as *triactome*. Triactome-targeted pharmacology may provide a novel therapeutic approach in cardiovascular disease.

Keywords: adipose tissue, adipokines, atherosclerosis, lymphocytes, mast cells, NGF, BDNF, perivascular nerves

22 FT Rančić G, Fiore M, Pancheva R, Tunçel N, Beltowski J, Zhelezov M, Ghenev P, Hinev A, Panayotov P, Evtimov N, Yanev S, Tonchev A, Aloe A, Chaldakov GN. Adipose tissue: The renaissance marked by four paradigm shifts. *Adipobiology* 2014;6:48-53

One of the biggest recent achievements in the study of cardio-metabolic diseases (atherosclerosis, hypertension, obesity, type 2 diabetes mellitus, metabolic syndrome, and Alzheimer's disease, which is recently viewed as type 3 diabetes, see below) is associated with the "rediscovery" of a neglected tissue, the adipose tissue.

Here we will *Dance Round* four paradigm shifts in the study of adipose tissue.

In 1962, Thomas S. Kuhn published his book *The Structure of Scientific Revolutions* (1st edition, University of Chicago Press, Chicago, USA). Its publication was a landmark event in the history and philosophy of scientific knowledge (epistemology). Kuhn challenged the prevailing view of "normal science" which

was viewed as "development-by-accumulation" of accepted facts and concepts leading - most often - to *epistemological paralysis*, we dubbed it neophobia (the term also used for children above the age of 1 year). Kuhn argued for a model in which a period of such conceptual continuity in normal science were interrupted by a period of revolutionary science leading to a new paradigm, an event he designated *paradigm shift*.

At epistemological level, the adipose tissue has undergone four major paradigm shifts in last 20 years, which "upregulated" it above the horizon. Consequently, adipose tissue takes center stage in so many diseases that it leaves most scientists and medical doctors astonished.

23 FT PI Ghenev. Correlation is not causation: Probable role of immunization with bacillus Calmette Guerin vaccine in atherogenesis. *Adipobiology* 2014;6:45-47

In spite of the enormous volume of research in atherosclerosis, the etiological understanding of atherogenesis is still beyond compare. The Framingham Heart Study (started 1948) (1) identified the major risk factors and this concept has become an important part of the modern medical knowledge and has led to effective preventive strategies in clinical practice. But correlation is not causation. In an attempt to identify etiological factors and the immune mechanisms in atherogenesis, Georg Wick and his co-workers in a series of experiments obtained intriguing results, which confirm that atherosclerosis may be induced in rabbits by treatment with a variety of agents containing heat-shock protein of molecular weight 60 kD (HSP60) (2-7).

24 FT Spasova S, N. Petrova, P. Ghenev. HER2 expression in renal cell carcinoma. *Trakia J Sci*, 2015; 13 Suppl. 2: 141-143 doi:10.15547/tjs.2015.s.02.029

ABSTRACT

Renal cell carcinoma (RCC) is the most common malignancy of the adult kidney. A variety of proteins have been investigated for their use as prognostic tumor markers. At present, there are conflicting reports concerning HER2 expression in RCC.

PURPOSE: The aim of this study is to evaluate the expression of HER2 protein in patients with renal cell carcinoma (RCC) and to determine the relationship between the tumor grading, staging and the type of the tumor.

METHODS: The expression of HER2 in renal cell carcinoma was studied using immunohistochemical methods in paraffin-embedded specimens from 34 patients. Of these cases, 19 patients had clear cell carcinoma, 6 had chromophobe, 5 had papillary, and 4 had urothelial renal carcinoma. Nine of the patients had metastases (in regional lymph nodes and distant), 25 patients were without metastases. The membranous staining of HER2 was assessed as positive when the score was higher than 2 (0, 1 – negative, 2, 3 – positive), according to the well accepted scoring system for breast cancer.

RESULTS: The results showed that there were varying degrees of HER2 expression in different RCC's histological types. The same changes in HER2 expression can be seen in the tumors with and without metastases. There was no significant association between HER2 overexpression and tumor stage, grade and the type of tumor. The results of the present study point out the necessity to discuss eventual beneficial effect of Herceptin therapy.

Key words: renal cell carcinoma, HER2, immunohistochemistry

25 FT Kitanova M, Ghenev P. Chronic cold exposure: a white adipose tissue browning factors. *Adipobiology* 2015;7:43-45

In the human body, there are two major subtypes of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT). Using ¹⁸F-fluorodeoxyglucose (FDG), an intravenously administered radioactive glucose analog, it was demonstrated with positron emission tomography and computed tomography that the main BAT depots were disseminated throughout the human body (around the thoracic aorta, common carotid artery, brachiocephalic brachiocephalic artery, kidney, adrenal glands, liver, pancreas; in anterior mediastinum, supraclavicular fossa, axilla and thoracic paravertebral loci, also between neck muscles). The magnitude of FDG uptake by BAT was reported to increase with exposure to low temperature (1-4), hence cold exposure being considered one of the major browning factors (the myokine and adipokine irisin as well as other browning factors are not in the scope of present *Dance Round*).

26 FT Konsoulova A, Donev I, Conev N, Draganova S, Chervenkov T, Petrova N, Dimitrova E, Ghenev P, Kashlov Y, Kaley D. First line 5-fu-based chemotherapy with/without bevacizumab for metastatic colorectal cancer: one center experience results. *Scr Sci Medica* 2015; 47(Suppl 1): 20-25

ABSTRACT

Purpose: Colorectal cancer is the second leading cause of cancer mortality in the United States. According to the National Institute of Statistics in Bulgaria for 2012 there have been 2370 newly diagnosed colon cancer and 1664 rectal cancer cases and the total number of registered patients is 29995. Adding Bevacizumab to chemotherapy in patients with metastatic colorectal cancer improves progression-free survival but yet no predictive markers for patient selection have been described and proved in the clinical practice. In our study we examined two plasma biomarkers that may correlate with response to first line Bevacizumab containing chemotherapy in patients with metastatic colorectal cancer.

27 FT Popov H, P. Ghenev. Expression of CD10 as a prognostic and predictive factor in urothelial carcinomas. *Trakia J Sci*, 2015; 13 Suppl. 2: 144-146 doi:10.15547/tjs.2015.s.02.030

ABSTRACT

Purpose: The aim of the study is to compare the expression of CD10 in invasive and non-invasive urothelial carcinomas.

Methods: Primary sites of 40 cases of urothelial carcinomas were studied on H&E stained sections from the original biopsy paraffin block, out of them, 20 - with and another 20 – without smooth muscle invasion. For CD 10 expression routine immunohistochemical procedure was applied, using DAKO FLEX monoclonal mouse antihuman clon 56C6.

Results: Two groups - invasive and non-invasive urothelial cancers were compared in regard to CD10 expression. The results definitely reveal that most of the cells in all invasive cancers express CD10, while in non-invasive cancers CD10 expression was absent.

Conclusion: The results provide convincing evidence for CD10 role in urothelial cancer invasiveness in underlying smooth muscle.

Key words: CD10, urothelial carcinoma, invasive

28 FT Pavlov S, Ivanova I, Popov H, Tzaneva M, Ghenev P. A rare comorbidity: dermatitis herpetiformis and sarcoidosis - a case report. *Serbian J Dermatol Venerol* 2016; 8 (3): 171-176.

Abstract

Sarcoidosis is an enigmatic, multisystem granulomatous disease of unknown etiology and wide range of clinical presentations. Case report: A 54-year-old female presented with facial rash: polymorphic, round, infiltrated erythematous plaques, 1 - 3 cm in size, disseminated on several areas of the face. The medical history was consistent with dermatitis herpetiformis and persistent intrahepatic cholestasis. The laboratory test results suggested celiac disease (strong positivity of IgA anti-tissue transglutaminase antibodies) but upper endoscopy was not performed to confirm it. The skin biopsy revealed noncaseating epithelioid-cell granulomas, and negative direct immunofluorescence showed IgA deposits in the dermis. Sarcoidosis with cutaneous and hepatic involvement was established based on compatible clinical findings and supportive histology. The period between manifestations of Dühring disease and skin manifestations of sarcoidosis was 20 years. Conclusion: Our clinical case supports the hypothesis for common immune pathogenic factors in gluten-sensitive diseases and sarcoidosis. The simultaneous occurrence of celiac disease and sarcoidosis is rare, but should not be under recognized.

Key words

Sarcoidosis; Dermatitis Herpetiformis; Comorbidity; Wheat Hypersensitivity; Diet, Gluten-Free; Epithelioid Cells; Granuloma;

29 FT Кашлов Я, В. Вълков, И. Щерев, Й. Донева, А. Киркорова, Н.Цонев, Л. Иванова, П.Генев, Т.Радева, Ж.Георгиева. Роля на НМGB1в патогенезата на миокардния инфаркт. Диагностични и прогностични аспекти. *Наука Кардиология* 2016 (4):175-178

ABSTRACT

PURPOSE: Recently new roles for vitamin K, different from that in coagulation, have been proposed, including prevention of cardiometabolic diseases. It was the aim of the present work to evaluate the impact of vitamin K treatment on the changes in liver and pancreas of rats with experimentally induced metabolic syndrome.

METHODS: Four groups of rats were used, as follows: one control group fed regular rat chow; one group fed high fat, high fructose (HFHF) diet for 12 weeks to induce a metabolic syndrome (MS) and two groups with MS treated with vitamin K1 and K2 respectively. At the end of the experiment, liver tissue and pancreas were dissected out for morphological examination.

RESULTS: All groups of rats fed HFHF diet expressed liver histological changes consistent with steatosis. These alterations were more pronounced in the groups treated with vitamin K2 and K1. The pancreatic tissue of the HFHF fed animals showed similar degree of lipomatosis irrespective of treatment.

CONCLUSIONS: In rats with diet-induced MS, treatment with vitamin K1 and K2 did not produce the expected morphological evidence of improvement, even tended to aggravate the liver changes. These results disagreed with other effects of vitamin K that were established.

Key words: Vitamin K, liver steatosis, pancreatic lipomatosis, rats, high-fat-high-fructose diet

30 FT Kitanova M, Popov H, Gancheva S, Zhelyazkova-Savova M, Galunska B, Ghenev P. Effects of vitamin K on liver steatosis and pancreatic lipomatosis in experimental model of metabolic syndrome. *Trakia J Sci*, 2016; No4, pp 351-355.

Въведение

Разпространението на исхемичната болест на сърцето и сърдечната недостатъчност достига 8% в западните страни и е причина за повече от 30% за смъртността¹. Доказа се, че най-ефективната стратегия за лечение на една от формите на исхемичната болест – остър инфаркт на миокарда, е незабавна реперфузия с първична перкутанна коронарна ангиопластика (PCI)^{2, 3}. Въпреки това, пациентите, преживели остър миокарден инфаркт, имат 10% по-висок риск от смърт и 25% по-висок риск да развият сърдечна недостатъчност в рамките на една година от инцидента⁴. Пациентите с миокарден инфаркт със ST-елевация (STEMI), лекувани с първична ангиопластика или с тромболитични средства, са изложени на риск след реперфузия на исхемичната зона да развият миокардна реперфузионна увреда (I/R injury)⁵⁻¹⁰. Парадоксално, I/R увредата може да ограничи благоприятния ефект от ангиографски извършената успешна реперфузия на миокарда. Съ-

31 FT Konsoulova A, Donev I, Conev N, Draganova S, Petrova N, Dimitrova E, Popov H, Bratoeva K, Ghenev P. First line 5-fu-based chemotherapy with/without bevacizumab for

metastatic colorectal cancer: tissue biomarker candidates. J IMAB. 2016 Jan-Mar;22(1):1039-1044.

DOI: <http://dx.doi.org/10.5272/jimab.2016221.1039>

ABSTRACT

Purpose: Colorectal cancer is the second leading cause of cancer mortality in the USA. According to Bulgarian National Statistics Institute, 2370 colon and 1664 rectal cancer cases were diagnosed in 2012 with total number of patients 29995. Adding bevacizumab to chemotherapy in patients with metastatic disease improves progression-free survival (PFS) but no predictive markers have been proven in the clinical practice. In our study we examined two tissue biomarkers that may correlate with response to bevacizumab-containing chemotherapy in patients with metastatic colorectal cancer.

32 FT S.Yanev, M.Fiore, A.Hinev, P.Ghenev, M.Hristova, P.Panayotov, A.B.Tonchev, N.Evtimov, L.Aloe, G.Chaldakov From Antitubulins to trackins Biomedical Reviews 2016 ISSN 1314-1929

Microtubules (MT) are dynamically instable, assembling and disassembling structures of the cell. Tubulin, the major building protein of MT, is a heterodimer consisting of α and β subunits. Agents that bind to tubulin and inhibit its assembly lead to the inhibition of MT formation. Such tubulin-binding agents are usually termed MT-disassembling agents or antitubulins. Endocytosis, matrix protein secretion, cell division, cell migration and inflammation are examples of MT-dependent processes. Their dysfunction, in particular in arterial smooth muscle cells (ASMC), is critically involved in atherogenesis. Here we Dance round (i) MT-based secretory pathway in ASMC and, in turn, antitubulins for atherosclerosis therapy, and (ii) the neurotrophins, particularly nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) and their receptors Trk (tyrosine receptor kinase; pronounced "track"), introducing the term trackins – Trk-targeting agents (TTA) that influence positively (agonistically) or negatively (antagonistically) the activity of TrkA receptor for NGF and/or TrkB receptor for BDNF. We propose that some trackins and their native ligands may have therapeutic potentials for cardiometabolic, neuropsychiatric, oncologic and other diseases. Finally the interaction of MT-tubulin and neurotrophin Trk receptors is outlined.

Biomed Rev 2016, 27: 59-67

Key words: microtubules, tubulin, colchicine, NGF, TrkA, BDNF, TrkB, disease

33 FT Ghenev P, Kitanova M, Popov H, Evtimov N, Stoev S, Tonchev A, Chaldakov G. Neuroadipobiology of arrhythmogenic right ventricular dysplasia. An immunohistochemical study of neurotrophins. Adipobiology 2016; 8: 55-58.

Abstract

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited disorder of cardiomyocyte-to-cardiomyocyte adhesion proteins associated with ventricular arrhythmias and sudden cardiac death. It is characterized by progressive fibrofatty replacement of right ventricular myocardium. The presence of adipose tissue either with or without fibrous tissue, scattered among cardiomyocytes is the histological hallmark of the disease. Being in the myocardium, adipocytes trigger damage to cardiomyocytes, thus causing electrical instability of the right ventricular myocardium, but the molecular pathogenesis of such an electrical instability in ARVD is still unclear. Since (i) adipose tissue replacement of cardiomyocytes is the most essential histological finding in ARVD, (ii) nerve growth factor (NGF) exerts an arrhythmogenic effect related to sudden cardiac death, and (iii) adipose tissue produces NGF and brain-derived neurotrophic factor (BDNF), the aim of the present study is to analyze immunohistochemically ARVD-related adipocytes with special attention to the expression of NGF and related neurotrophins, BDNF and neurotrophin-3 (NT-3) and their respective TrkA, TrkB and TrkC receptors. Eight cases with ARVD were autopsy proven. The present results demonstrate that the intramyocardial adipocytes and cardiomyocytes in ARVD express NGF/TrkA and NT-3/TrkC, suggesting that they may play a substantial part in life-threatening myocardial electrical instability.

Adipobiology 2016, 8: 55-58

Key words: arrhythmogenic right ventricular dysplasia, adipose tissue, NGF, BDNF, NT-3, Trk receptors

34 FT Stoyanov GS, Dzenkov D, Ghenev P. Cytokeratin AE1/AE3 mimicry in glioblastoma. Scripta Sci Med 2017;49 (Suppl 1):47-52 10.14748/ssm.v49i1.2055

ABSTRACT

INTRODUCTION: The diagnosis and treatment of intracranial tumors requires a multidisciplinary approach. A key moment in this process is the pathological verification of the tumor type. This process, although aided by immunohistochemistry (IHC), can often be difficult and misleading.

MATERIALS AND METHODS: Ten histologically confirmed cases of glioblastoma multiforme (GBM) were reviewed for their IHC reaction with the anti-gliial fibrillary acidic protein (GFAP) glial marker and the CK AE1/AE3 antibody cocktail, whose main use in neuropathology is to either prove or rule out metastatic cancer of epithelial origin, the primary location of which may not be known or even suspected.

RESULTS: All ten pathologically verified cases of GBM were diagnostically positive for GFAP, with eight of them also revealing CK AE1/AE3 expression with variable intensity. Out of the CK AE1/AE3 positive cases, five (50% in total) gave a low to intermediate non-diagnostic positive reaction, while the other three cases (30% in total) gave a strong positive reaction with possible diagnostic value. Cells, across all GBM cases, that tested positive for CK AE1/AE3, regardless of the strength of the reaction, were also positive for GFAP on neighboring IHC serial slides.

CONCLUSION: The presented results reveal CK AE1/AE3 expression in a great portion of GBM cases, which may be caused by three-dimensional mimicry between the CK AE1/AE3 and GFAP target molecules. This therefore necessitates the need for a careful interpretation of the results. CK AE1/AE3, however, remains a useful tool in neuropathology, regardless of the possibility of false positivity in GBM cells.

Keywords: glioblastoma, IHC, CNS tumor, antigene mimicry

35 FT Stoyanov GS, Kitanova M, Dzenkov DL, Ghenev P, Sapundzhiev N. Demographics of head and neck cancer patients: A single institution experience. Cureus. 2017 Jul 2;9(7):e1418. doi:10.7759/cureus.1418. PMID:28875091

Abstract

Introduction

Head and neck cancer (HNC) comprises a diverse group of oncological entities, originating from various tissue types and organ localizations, situated in the topographical regions of the head and neck (H&N). This single institution retrospective study was aimed at establishing the HNC patient demographics and categorizing the individual incidence of H&N malignancies, regarding their organ of origin and main histopathological type.

Materials and methods

All histologically verified cases of HNC from a single tertiary referral center were reviewed in a descriptive retrospective manner. Data sampling period was 47 months.

Results

Male to female ratio of the registered HNC cases was 3.24:1. The mean age of diagnosis was 63.84 ± 12.65 years, median 65 years. The most common HNC locations include the larynx 30.37% (n = 188), lips and oral cavity 29.08% (n = 180), pharynx 20.03% (n = 124) and salivary glands 10.94% (n = 68), with other locations such as the external nose, nasal cavity and sinuses and auricle and external ear canal harboring a minority of the cases. The main histopathological groups include squamous cell carcinoma 76.74% (n = 475) and adenocarcinoma 6.14% (n = 38), with other malignant entries such as other epithelial malignancies, primary tonsillar, mucosa-associated lymphoid tissue or parenchymal lymphomas, connective tissue neoplasias, neuroendocrine and vascular malignancies diagnosed in a minority of cases.

36 FT Stoyanov GS, Dzhenkov DL, Kitanova M, Ghenev P, Tonchev AB. Demographics and incidence of histologically confirmed intracranial tumors: A five-year, two-center prospective study. *Cureus* 2017; 9(7): e1476. doi: 10.7759/cureus.1476. PMID:28944115

Abstract

Introduction

Intracranial tumors (ICTs) are a diverse group of malignancies that pose an immediate threat to patients' lives, no matter their local or metastatic origin, benign or malignant nature. These lesions have severe clinical courses and need to be diagnosed and treated as soon as possible, with pathological verification being the pivotal moment in the process of determining curative modalities.

Aim

The aim of this study was to compare the incidence of histologically confirmed ICTs in Eastern Bulgaria, based on their type (primary, metastatic, and non-volume occupying lesions (NVOL)), their respective subtypes, and incidence in a descriptive manner.

37 FT Stoyanov GS, Dzhenkov D, Kitanowa M, Donev IS, Ghenev P. Correlation between Ki67 grade and World Health Organization grade and patient survival in glial tumors with astrocytic differentiation. *Cureus* 2016; 9(6): 1-9 e1396. DOI: 10.7759/cureus.1396

Abstract

Background

Glioblastoma multiforme (GBM) is a class IV astrocytic tumor, the most malignant of the four groups of World Health Organization (WHO) tumors with astrocytic differentiation.

Aim

The aim of this study was to establish whether a correlation exists between the Ki-67 index of tumors with astrocytic differentiation, WHO grade, and patient survival.

Materials and methods

A retrospective non-clinical approach to patient selection was chosen for the aim of the study. A total of 47 patients diagnosed and treated for CNS tumors with astrocytic differentiation in the St. Marina University Hospital, Varna, Bulgaria, from September 2012 to July 2016 were retrospectively included into the study cohort. The cases were tested for their immunohistochemistry (IHC) reaction with Ki-67 after their original Hematoxylin and Eosin and IHC slides were reviewed by a single author and blind coded. The Ki-67 positivity index of the nuclei was estimated after digitalization of the slides and calculated by the ImmunoRatio automated counting tool. The individual Ki-67 index and patient survival of each case were statistically compared.

38 FT Stoyanov GS, Dzhenkov D, Ghenev P. The great imitator – EMA positive glioblastoma multiforme. *Scripta Sci Med* 2017;49(1):21-25

ABSTRACT

INTRODUCTION: Glioblastoma multiforme (GBM) has always been a diagnostic challenge for pathologists. As a rare oncological entity with astrocytic differentiation, it can manifest itself in a variety of histomorphological forms, mimic other tumors and it often has varying immunohistochemical (IHC) profiles, further challenging the process of its verification.

MATERIALS AND METHODS: Four pathologically verified cases of GBM, registered at the St. Marina University Hospital, Varna, Bulgaria were retrieved from the central pathological archive. The cases were tested and reviewed based on their hematoxylin and eosin (H&E) profiles and IHC reactions with GFAP used as a glial differentiation marker, Vimentin - as a positive IHC control and EMA, an epithelial marker, non-reactive in healthy brain tissue.

RESULTS: As expected all GBM cases had the histomorphological hallmarks of the tumor on the H&E stain. They were diagnostically positive for GFAP and had a strong positive IHC reaction with Vimentin. Three out of the four cases also revealed a varying in intensity reaction with EMA, with one case having a weak reaction in individual cells that could not be considered diagnostic and the other two cases having a diffuse positive reaction in most of the tumor cells.

39 FT Rancic G, Petrovic A, Sekulovic-Stefanovic L, Boyanic V, Ghenev PI. Adipotopography: TOFI versus TOTI, or a hidden Homo obesus. *Proc I International Symp Adipobiology and Adipopharmacology*, 2007;13-14

Abstract

The white adipose tissue is located in (i) two large depots - subcutaneously and abdominally -, which are well-visible, and (ii) multiple small depots, which are invisible without using imaging technologies (echography, computed tomography and alike). Small adipose depots are located around the heart, blood vessels, pancreas, ovaries, prostate gland, and lymph nodes, also in the breast. Recent imaging studies demonstrated the presence of four major subphenotypes in internal adipose tissue distribution: TOTI (thin outside, thin inside), FOFI (fat outside, fat inside), FOTI (fat outside, thin inside) and TOFI (thin outside, fat inside), the latter may be considered an "invisible" or hidden expression of *Homo obesus*. Current thinking indicates that body mass index over 20–25 kg/m² should be considered as a "classical" anthropometric criterion for overweight and/or obesity. Briefly, being lean outside does not mean you are not obese inside.

Adipobiology 2017, 9: 57–60

Keywords: adipose tissue, adipobiology, obesity, body mass index

40 FT Stoyanov GS, Kobakova I, Stoyanov D, Zhelezov M, AngelovaM, Dzenkov D, Georgieva R, Ayetola L, Kovachev E, Ghenev P, Tonchev AB. Early second trimester spontaneous miscarriage due to fourth ventricle choroid plexus papilloma. J Fetal Med. <http://doi.org/10.1007/s40556-018-0175-1>

Abstract Miscarriage due to fetal tumors is an extremely rare finding, with a varying incidence from 1.7 to 13.5 per 100,000 live births, with central nervous system tumors occupying a minority of these cases. Herein, we report the gross morphological and histological findings of a 17-gestational week spontaneous miscarriage in a 27 year old multi-gravida due to a fourth ventricle choroid plexus papilloma (CPP). The CPP was composed of a pronoun fibro-vascular stroma covered with a dense lining of tall cuboid sparsely ciliated single cell layer with rich in chromatin nuclei. The cytoplasm of the CPP covering cells was intensely colored when compared to the pale cytoplasm of the covering cells of the choroid plexus collected from the lateral ventricle, which also lacked in such pronoun fibrovascular stroma. The fourth ventricle was significantly dilated with parenchymal compression of nervous tissue towards the chondral fetal cranium.

41 FT P.I.Ghenev, G.Rancic, P.Panayotov, M.Fiore, A.B.Tonchev, N.Tuncel, N.Wvtimov, S.Yanev, L.Aloe, G.N.Chaldakov Quo vadis, atherogenesis? Part 2. Tunica adiposa – the new player in the process of atherogenesis *Adipobiology* 2017; 28: 134-138.

Abstract

Today, atherosclerosis is considered an immune-mediated inflammatory disease featured by endothelial dysfunction (intimal thickening), medial atrophy, and adventitial lesions associated with adipose dysfunction. Since Rudolf Virchow's time when the intima has been considered the most important vascular area involved in atherogenesis, our views on this multiplex phenomenon are indeed changing. Here we *Dance round* an emerging role played by perivascular adipose tissue (*tunica adiposa*) in the process of atherogenesis. We intend to integrate the traditional "inside-out" (intimal and medial) to an "outside-in" (adventitial and adipose) pathway of atherogenesis.

Adipobiology 2017, 9: 61–64

Keywords: atherosclerosis, adipose tissue, *tunica adiposa*, integrative approach

42 FT Chaldakov GN, Ghenev PI. Colchicine, inflammation and fibrosis in cardiovascular disease: merging three classical tales. *Biomed Rev* 2017; 28: 105-110

ABSTRACT

*Colchicine, isolated from Colchicum autumnale, is a drug for acute gouty arthritis known from thousands of years whose use has survived to modernity. Over the past decades, the use for this very old drug extended beyond gout therapy. This was due to the advance in knowledge of (i) association of hyperuricemia and gout with cardiovascular disease, (ii) cytoskeletal microtubules (MT), and (iii) anti-inflammatory and antifibrotic effects of colchicine, a classical MT-disassembling agent (antitubulin). Here, we present the Bulgarian contribution to colchicine potential in the therapy of cardiovascular disease that has emerged in the early 1970's in the Laboratory of Electron Microscopy, Medical Institute, Varna, Bulgaria, studying the secretory (fibrogenic) function of vascular smooth muscle cells. From this time onward, low-dose colchicine (LoDoCo, 0.5 – 1.0 mg/daily) was increasingly administered orally for therapy of cardiovascular disease such as acute coronary syndromes, cardiac surgery postoperative atrial fibrillation, pericarditis, cardiac hypertrophy-associated heart failure, and systemic necrotizing vasculitis. Thus colchicine might be a new tool in the present therapeutic armamentarium for these diseases. It is simply an example of MT-disassembling drugs. Further studies will definitely be required before gaining real confidence in this kind of antitubulin therapy. This may lead to developing new and more specific antitubulins for therapy of cardiovascular disease. *Biomed Rev* 2017; 28: 110-115.*

Keywords: microtubules, tubulin, colchicine, antitubulins, cardiovascular diseases, inflammation, fibrosis

43 FT Ghenev PI, Aloe L, Kischeva AR, Singh M, Panayotov P, Fiore M, Chaldakov GN. Quo vadis, atherogenesis? Part 1. Smooth muscle cell secretion – how foe becomes friend in the fight against the atherosclerotic plaque. *Biomed Rev* 2017; 28: 134-138.

ABSTRACT

*Atherosclerosis is a chronic inflammatory disease in which exacerbation leads to myocardial infarction, stroke and/or lower limb ischemia. Phenotypic plasticity of artery smooth muscle cells (SMC) that can adapt to changes in the injured arterial microenvironment is a major determinant of atherosclerotic plaque vulnerability. Plaque instability has been associated with the ulceration or rupture of the fibrous cap composed primarily of SMC and collagen and elastin fibers, that covers the lipid core of the plaque. In this scenario, we, together with SMC, Dance round recent advances that have shed light on the relationship between inflammation, fibrosis and plaque vulnerability and stability. Specifically, we have addressed the question of how the secretory (fibrogenic) activity of SMC occurring within the plaque may become a plaque stabilizer (a friend). We describe a new paradigm shift in the cell biology of atherosclerosis that relates the inhibition of SMC matrix secretion and proliferation (the classical way for reducing plaque size) to the stimulation of these processes (the new way aimed at the plaque stabilization by increasing the thickness of its fibrous cap). Briefly, an increased secretion of matrix molecules, particularly collagen and elastin, by SMC could “shift” them from foe to friend in the fight against the vulnerable atherosclerotic plaque. *Biomed Rev* 2017; 28:134-138.*

Keywords: atherosclerotic plaque, fibrous cap, smooth muscle cells, macrophages, phenotypic modulation, matrix proteins, inflammation, fibrosis, colchicine

44 FT Спасова С, Генеv П. Корелация между туморната коагулационна некроза и клиничко-патологични параметри при светлоклетъчен карцином на бъбрека. Варненски медицински форум, 2018; 7 (1): 29-34

РЕЗЮМЕ

Въведение: Туморната некроза (ТН) многократно е свързана с по-големия размер на туморите, по-ниска диференциация и по-висока пролиферативна активност и въпреки че патогенезата ѝ остава до голяма степен неизвестна, се смята, че тя представлява индиректен маркер за по-агресивно биологично поведение на тумора.

Цел: Целта на проучването е да се изследва наличието на некротични участъци в метастатичен и неметастатичен светлоклетъчен карцином на бъбрека и да се анализира корелацията им с клиничко-патологични параметри.

45 FT Stoyanov G S, Sarraf J S, Matev B K, Dzhankov D, Kitanova M, Iliev B, Ghenev P, Tonchev AB, Enchev Y, Adami F, De Carvalho LEW. A comparative review of demographics, incidence, and epidemiology of histologically confirmed intracranial tumors in Brazil and Bulgaria. *Cureus* 2018;10(2): e2203. DOI 10.7759/cureus.2203

Abstract

Intracranial tumors (ICTs) attract numerous scientific teams and tremendous financial resources worldwide. These lesions of the central nervous system (CNS) can be both benign and malignant in biological behavior as well as local or metastatic in origin. We compared data from two studies on primary and metastatic ICTs from Brazil and Bulgaria, based on histopathologically confirmed ICTs from tertiary health centers. Primary ICTs significantly outweigh the frequency of metastatic ICTs. Primary ICTs represent 86.45% in Brazil and 69.17% in Bulgaria, with around 60% of their totals being malignant. There is a statistical dominance of tumors from the neuroepithelial origin, with the most common entry being glioblastoma multiforme. The second-most common primary ICT group comprises tumors of meningeal origin. Metastatic ICTs show great variance; 13.55% in Brazil and 31.38% in Bulgaria of all ICT cases being attributed to them. However, metastatic ICTs are even a more diverse group than neuroepithelial tumors, with the majority of this group comprising metastatic colorectal adenocarcinoma (almost exclusively in males), metastatic breast adenocarcinoma in females, metastatic pulmonary carcinomas (primarily from the non-small cell group with a male predominance), and metastatic melanoma with an even gender ratio.

46 FT Н Цонев, И Донев, Т Червенков, А Консулова, П Генев, Е Димитрова, Д Калев.
Влияние на Микрорибонуклеинови киселини върху сигнални клетъчни пътища при колоректален карцином Списание на Българското Онкологично Дружество 2012;1: 44-48
ISSN 1312-6601

РЕЗЮМЕ

Микрорибонуклеиновите киселини (миРНК) са малки РНК-молекули, изградени от около 21-25 нуклеотида, които не кодират протеини, но имат важна функция за регулиране на генна експресия чрез свързване с комплементарни 3'нетранслирани области (3'UTR) на информационна РНК. До този момент са открити хиляди миРНК в различни растения, животни и микроорганизми. Натрупани са редица доказателства за участие на миРНК в разнообразни биологични процеси, като регулатори на клетъчна пролиферация, диференциация, апоптоза и други явления, свързани с онкогенезата, в това число и при колоректален карцином (КРК).

Цел на този обзор е дискутира възможностите на миРНК за регулиране на онкогенни и тумор-супресорни сигнални пътища, участващи в патогенезата на КРК.

Резюмета:

1 A Hinev A, Fukuda M, Ghenev P, Mizokami A, Miwa S, Konaka H, Koshida K, Namiki M.
Clinical utility of prostate specific antigen and cytokeratin immunohistochemical expression in male pelvic malignancies. World Congress of Surgery, Praga, Czech Republic, 7-10 September, 2005



AIM

To evaluate the clinical utility of prostate specific antigen (PSA) and cytokeratin (CK) immunohistochemical (IHC) expression in prostate cancer and other male pelvic malignancies.

MATERIAL & METHODS

72 male patients who underwent surgery for prostate cancer, bladder cancer, or colorectal cancer, entered the study. Beside the primary tumors, metastatic lesions (lymph nodes and bone) were analyzed, as well.

145 archive paraffin blocks and 21 fixed in formalin biopsy specimens were initially used.

A standard IHC protocol, including the primary antibodies ER-PR8 (anti-PSA), AE1/AE3 and HMW 34 β E12 (anti-CK), and the reagents of the DAKO Envision + visualization system, was used.

2 A Tonchev AB, Stankulov IS, Ghenev PI, Pavlov PS, Chaldakov GN, Yamashima T. Identification of putative progenitor cells in the anterior subventricular zone of the adult human brain. C R Bulg Acad Sci 2006; 59; 683-686.

Мозъкът на бозайниците, дори и след полова зрялост, запазва, макар и ограничена, регенераторна способност, осъществявана от прогениторни клетки, локализирани в поне две обособени зони: субвентрикулярна зона по протежение на предния рог на латералния мозъчен вентрикул, и субгрануларна зона на хипокампалия *gyrus dentatus*. През последното десетилетие, тези клетки станаха обект на интензивни фундаментални проучвания с основна цел тяхното приспособяване като ефективна клетъчна терапия на многообразието от мозъчни заболявания, протичащи с невронална загуба. За да изследваме поведението на ендегенните прогениторни клетки в максимално близки условия до тези на човешкия мозък, ние използвахме приматен модел за мозъчни изследвания при маймуни, сравнявайки нормални с исхемични условия. Нашите резултати показват, че в мозъка на приматите се съдържат ендегенни прекурсори, които реагират на исхемия, увеличавайки своята пролиферация. Ние създадохме мозъчна "карта" на регионите, в които прекурсорната пролиферация се увеличава от исхемичната увреда, както и на фенотипа на зрелите клетки, генерирани от прогениторите. Ние определихме молекули, които потенциално участват в прекурсорната регулация. Наличните резултати показват, че приматният мозък притежава ендегенна репаративна способност, терапевтичното потенциране на която би могло да доведе до клинично приложими резултати в лечението на мозъчни разстройства, протичащи с клетъчна смърт.

Ключови думи: мозъчни прогенитори, примати, церебрална исхемия

3 A Kornovski I, Genev P. Surgical treatment of fallopian tube carcinoma with metastases in the pelvic peritoneum, cervix uteri (septum rectovaginale), and the colon transversum. Akusherstvo i ginekologiya 2007; 46 (8), pp. 27-31

ХИРУРГИЧНО ЛЕЧЕНИЕ НА КАРЦИНОМ НА МАТОЧНАТА ТРЪБА С МЕТАСТАЗИ ПО ТАЗОВИЯ ПЕРИТОНЕУМ, МАТОЧНАТА ШИЙКА (SEPTUM RECTOVAGINALE) И COLON TRANSVERSUM

Я. Корновски, Генев П.

МБАЛ "Света Анна" АД, гр. Варна, Гинекологична клиника
МУ Варна, Катедра по патология

Резюме. Представен е случай на 66 год. пациентка с карцином на лява маточна тръба, имплантационни метастази по перитонеум, colon transversum, тазови лимфни възли, оментум и septum rectovaginale. Описано е хирургичното лечение и хистологичните данни, също така е представен кратък обзор на литературата по отношение на форми, диагноза и прогноза на карцинома на маточната тръба (КМТ).

Ключови думи: метастази, тазова перитонектомия, радикална хистеректомия, карцином на тръбата.

4 A Hinev A, Klissarova A, Ghenev P, Paunov S, Chaushev B, Chankov P, Anakievski D, Dyakov S, Kolev N, Deliiski T. Impact of pelvic lymph node dissection in high-risk prostate cancer. Urology 2008;72 (Suppl 5A): MP-3.06

MP-3.06

Impact of Pelvic Lymph Node Dissection in High-Risk Prostate Cancer

Hinev A¹, Klissarova A², Ghenev P³, Paunov S¹, Chaushev B², Chankov P¹, Anakievski D¹, Dyakov S¹, Kolev N⁴, Deliiski T⁴

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Introduction and Objectives: The role of pelvic lymph node dissection (PLND) in high-risk prostate cancer (HR PC) still remains controversial. The aim of the present study was to examine the lymph nodes (LN), collected during extended PLND in patients with HR PC, and to as-

5 A P. Panayotov, P.Ghenev, M. Fiore, L. Manni, V. Nikolova, A. Tonchev, L. Aloe, G. Chaldakov. Neurotrophins in vascular wall and perivascular adipose tissue of human coronary and internal thoracic arteries. 18th World Congress, World Society of Cardio-Thoracic Surgeons, Kos Island, Greece, April 30 – May 3, 2008

INTRODUCTION

- Neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), may act not only on neuronal cells but also on a variety of nonneuronal cells including vascular smooth muscle cells and immune cells.
- We have previously reported that serum levels of NGF and BDNF are reduced in patients with acute coronary syndrome (ACS) as compared to control subjects (Manni et al, 2005).
- We aimed to determine the neurotrophin vascular wall levels in coronary arteries (CA; atherosclerosis-prone vessels) or internal thoracic arteries (ITA; atherosclerosis-resistant vessels) obtained from autopsy cases with or without advanced atherosclerotic lesions.

6 А Генов П., Д.Дженков, А.Тончев, Г.Чалдъков. Роля на адвентицията и периаартериалната мастна тъкан в атерогенезата. Десети национален конгрес по патология, Хисар, 30 май, 2009

Д 43

РОЛЯ НА АДВЕНТИЦИЯТА И ПЕРИАРТЕРИАЛНАТА МАСТНА ТЪКАН В АТЕРОГЕНЕЗАТА

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Класическите теории за възникване и прогресиране на атеросклеротичните лезии са концентрирани върху значението на артериалната интима. В последните десетилетия се появиха литературни данни за ролята на артериалната адвентиция и периаартериалната мастна тъкан

7 А Дженков Д, Н Сапунджиев, П. Генов. Хистопатологични промени при синдром на празния нос. D. Dzhenkov, N. Sapundzhiev, P. Genev. Histopathological changes in empty nose syndrome. XIII Belinov's Symposium, Golden Sands, September 2012;37

ХИСТОПАТОЛОГИЧНИ ПРОМЕНИ ПРИ СИНДРОМ НА ПРАЗНИЯ НОС

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Цел: Синдромът на празния нос (СПН), описан за първи път 1994 от E.V. Kern, се проявява с парадоксална обструкция и назална сухота. Най-често е последица от агресивна ендоназална хирургия. Целта на настоящото проучване е да се опишат хистологичните промени при този синдром.

Материал и методи: Биопсични материали от пациенти със СПН са обработени според рутинната практика за хистологично изследване.

8 A Popov H, P Ghenev. Intraglomerular kidney metastases from chromophobe renal cell carcinoma. J Bulg Apheresis Assoc (BAA) 2013; 2: 40-41.

ИНТРА-ГЛОМЕРУЛНИ МЕТАСТАЗИ В БЪБРЕК ОТ ХРОМОФобен БЪБРЕЧЕН КАРЦИНОМ

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Наличието на метастатични туморни клетки в сегменти на бъбречни гломерули е рядко явление. Докладвани са единични случаи с интра-гломерулни метастази от плоскоклетъчен карцином на бял дроб и хранопровод, аденокарцином на панкреас, хематологични малигнени заболявания, мезотелиом на плеврата, и меланом. Описани са два модела на интра-гломерулни метастази (Wuketich, 1960): дифузно "intracapillary", при който туморните клетки растат дифузно във всички гломерулни туфи и дифузно "extracapillary" тип, при който париеталния епител на пространството на Бауман се заменя от туморните клетки.

9 A Ghenev P, H Popov. Morphological analysis of malignant renal tumors. J Bulg Apheresis Assoc (BAA) in cooperation with the Institute for Applied Nephrology, Aachen, Germany. 2013; II; 23

МОРФОЛОГИЧЕН АНАЛИЗ НА МАЛИГНЕНИ РЕНАЛНИ ТУМОРИ

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Честотата на малигнените ренални тумори нараства в световен мащаб. Голяма част от туморите се откриват в напреднал стадий и възможностите за терапевтично повлияване са сравнително ограничени. Целта на настоящото изследване е да се анализират морфологичните особености на реналните карциноми с оглед по-задълбочено стратифициране. Из-

10 A Kobakova I, Popov H, Dzhenkov D, Ghenev P. Large lipoma of the colon – a case report and a review of literature. *Adipobiology* 2012;4: 32.

Lipomas are frequently found benign tumors, originating from the white adipose tissue. They may be with variable size and located at any site in most organs and tissues. In the gastrointestinal tract, large lipomas are rare lesions, most frequently located in the colon and usually reported as incidental findings in 0.3-0.5% of cases in large autopsy series (1,2). A variety of clinical symptoms may be associated with lipomas, depending on their size and location in the gastrointestinal tract (3-5). The most common site for symptomatic solitary lipoma is the ascending colon, including the caecum, followed by the transverse colon, including both hepatic and splenic flexures, the descending colon, sigmoid colon and rectum. In the wall of the intestine, most lipomas are located in the submucosal space,

11 А Колова П, П Генев, Т Кондев. Параганглиом в областта на filum terminale. XI Национален конгрес по патология, Шумен, 2013; 55-56.

II 26

ПАРАГАНГЛИОМ В ОБЛАСТТА НА FILUM TERMINALE

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Параганглиома е невроендокринен тумор, обикновено капсулиран и доброкачествен, възникващ в специализирани нервни клетки свързани с автономни ганглии. В ЦНС, параганглиома почти изцяло се намира в cauda equina.

12 А Попов Х, П Генов. Сравнително морфометрично проучване на тумор-асоцираните тъканни мастоцити при рецидивиращи уротелни карциноми на пикочен мехур. XI национален конгрес по патология, Шумен, 2013; 43-44

II 16

СРАВНИТЕЛНО МОРФОМЕТРИЧНО ПРОУЧВАНЕ НА ТУМОР АСОЦИИРАНИТЕ ТЪКАНИ МАСТОЦИТИ ПРИ РЕЦИДИВИРАЩИ УРОТЕЛНИ КАРЦИНОМИ НА ПИКОЧЕН МЕХУР

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Описаните от Ерлих през 1878 год. мастоцити са имунни клетки, които реагират на стимули, освобождавайки биологично активни медиатори. От широкия спектър медиатори, които отделят някои имат стимулиращ, а други инхибиращ ефект върху злокачествените заболявания. Поставихме си за цел да изследваме разпределението на мастоцитите при уротелни карциноми. Да съпоставим техният брой в първичните тумори на нерцидивиращи и рецидивиращи карциноми. Изследвани са ретроспективно биопсични

13 А Генов П, М. Георгиева. Морфологични основи на персонализирана терапия на белодробен карцином. XI национален конгрес по патология, Шумен, 2013; 17

МОРФОЛОГИЧНИ ОСНОВИ НА ПЕРСОНАЛИЗИРАНА ТЕРАПИЯ ПРИ БЕЛОДРОБЕН КАРЦИНОМ

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Белодробният карцином продължава да бъде сред най-честите и най-тежко протичащите малигнени заболявания, въпреки огромният изследователски интерес. Предприетото преди години групиране дребно-/недребноклетъчен карцином вече не е достатъчно за нуждите на медицинската онкология. Много усилия, включително на хистологично ниво са насочени към стратифициране на карциномите с оглед намиране на звена в неопластичната трансформация и прогресия, подходящи за таргетна терапия. Големи надежди се възлагат и на генетичните изследвания. Целта на настоящето проучване е да се опишат морфологични особености, установени при 96 случая с белодробен карцином. Отчетени са хистологичните варианти и

14 А Попов Х, П Генов. Микроскопски особености на редки варианти на уротелните карциноми. XI национален конгрес по патология, Шумен, 2013; 46.

П 18

МИКРОСКОПСКИ ОСОБЕНОСТИ НА РЕДКИ ВАРИАНТИ НА УРОТЕЛНИТЕ КАРЦИНОМИ

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Туморите на пикочния мехур засягат най-често възрастта над 65 години. Заболеваемостта е 100 000:15.0 мъже и 3,3 жени. Наблюдава се тенденция за повишаване на заболяването, както и по-висока честота на считаните за редки варианти на уротелни карциноми. Представяме 3 случая на пациенти с рядко срещани варианти на уротелен карцином с под 5% честота според СЗО от 2004 година. Първи случай: жена на възраст 62 години с

15 A Zhelyazkova-Savova M, Galunska B, Gancheva S, Popov H, Kitanova M, Genev P. Effects of vitamin K on rats fed high-fat high-fructose diet. J Biomed Clin Res 2014, 7(1); Suppl. 1, p. 62

Summary

This study was undertaken to test the hypothesis that osteocalcin – a bone derived vitamin K dependent protein, plays an important role in carbohydrate metabolism and disorders.

In rats fed high-fat high-fructose (HFHF) diet to produce a metabolic syndrome, vitamin K1 and K2 were administered orally throughout the 12 weeks period of diet manipulation. Insulin tolerance test was performed at the end of the study. Behavioral tests for locomotion, anxiety, depression and memory were also carried out.

16 A Chaldakov GN, Aloe L, Tonchev A, Fiore M, Panayotov P, Rancic G, Nese T, Beltovsky J, Stoev S, Zhelezov M, Ghenev P, Hinev A, Evtimov N, Yanev S. Adipobiology: A research field marked by five paradigm shifts. Rom J Diabetes Nutr Metabol Dis 2015;22 Suppl 2: 13 +Adipobiology 2015;7:56

In this cardlight lecture we will start with a brief historical survey. Admittedly, the accumulation of adipose tissue (AT) was linked to obesity. This was known to Hippocrates, who stated that "sudden death is more common in those who are naturally fat than in the lean". Thomas Storr's book, *A Discourse Concerning the Causes and Effects of Corpulency* (1727), was the first English language manuscript on obesity. The adipocyte,

17 A Ghenev P, Kitanova M, Stoev S, Popov H. Arrhythmogenic right ventricular dysplasia: another example of adipose tissue related diseases – involvement of neurotrophins. Rom J Diabetes Nutr Metabol Dis 2015;22 Suppl 2: 20 +Adipobiology 2015;7:61

Arrhythmogenic right ventricular dysplasia (ARVD), also known as fatty degeneration of right heart, is a heritable disorder characterized by progressive degeneration and fibro-fatty replacement of right ventricular myocardium, causing electrical instability of the right ventricular myocardium, ventricular tachyarrhythmia and sudden death at a young age [1]. Several lines of evidence suggest that impairment of cardiomyocyte adhesions (desmosomal proteins) may be the underlying pathogenic mechanism *via* accelerating apoptosis of these cells [2],

18 А Гевев П, Попов Х, Щерев И. Морфологична хетерогенност при недребноклетъчен белодробен карцином. Национална конференция по патология, Трявна, 2015; 22.

Въпреки многобройните изследвания и вече постигнатите успехи, белодробният карцином продължава да бъде най-честият и тежко протичащ злокачествен тумор. Терапевтичните надежди, възлагани на генетичните изследвания и на лекарствените средства от групата на тирозин-киназните инхибитори на рецептора на епидермалния растежен фактор са донякъде помрачени от високия процент не отговарящи на лечението и бързо развиващата се резистентност. Целта на настоящето изследване е да бъдат изследвани различни морфологични показатели при 124 биопсични резекционни и некротични случая с оглед интерполиране на данните спрямо клиничното протичане.

19 А Янулова Н, Попов Х, Гевев П. Случай на склеродермия съчетана с вторична хемохроматоза. Национална конференция по патология, Трявна, 2015; 52-53.

Системна склероза е заболяване с неизвестна етиология, характеризиращо се с генерализирано фиброзиране на съединителната тъкан на дермата и интерстициалната съединителна тъкан на вътрешните органи. Представяме аутопсионен случай на 54-годишен мъж с разгърната клинична и морфологична картина на системна склеродермия, съчетана с вторична хемохроматоза. В конкретния случай приемаме хемохроматозата за вторична, поради липсата на отлагане на хемосидерин в кожата и анамнестичните данни за многократни хемотрансфузии. Съчетанието на двете заболявания води до

20 А Попов Х, Минкова В, Гевев П. Случай с light chain deposition disease – възможности на морфологична диагностика. Национална конференция по патология, Трявна, 2015;49-50

Заболяването с отлагане на леки вериги (Light chain deposition disease - LCDD) е сравнително ново и описано за първи път през 1976 год. при двама пациенти с краен стадий на бъбречно заболяване. Честотата на LCDD е неизвестна. Средният възраст при поставянето на диагнозата е 58 години

21 А Теодорова И, Бенкова М, Балеv Б, Попов Х, Гевев П, Икономов В. Бъбречно засягане при редки заболявания в дерматологията – клиничен случай. Петнадесета национална конференция „Диализа в 21 век“. 2015.

Голяма част от соматичните заболявания се съпътстват от кожни промени, които изискват намесата на дерматолог. В Европа около 30 мил. души страдат от редки генетични кожни заболявания – 6%-8% от общата популация. Булзната епидермолиза (БЕ) е рядко наследствено генетично заболяване, което се характеризира с абнормна реакция на кожата и лигавиците към механична травма. В България хората със заболяването са около 100 души. Приблизително 500 000 души в цял свят страдат от БЕ. По света наричат хората с булзна епидермолиза „леперудени хора“, а заболяването „леперудена болест.“ Лимитирани

22 A Spasova S, P. Ghenev. Xp 11.2 translocation renal cell carcinoma: a case report and a review of literature. Национална конференция, Плевен 2015

Introduction

Kidney carcinomas associated with Xp11.2 translocations / TFES gene fusions are present in the new version of the WHO classification of kidney tumors (2004). They are defined by a number of different translocations involving the Xp11.2 chromosome, all of them resulting from gene fusions involving the TFES gene. It is an uncommon tumor, whose morphology and biological behavior are not widely recognized as yet.

23 А Генеv П, Донеv И. Морфологични основи на таргетна терапия и лекарствена резистентност при белодробен карцином. XII Национален конгрес по патология, Велико Търново, 11 май 2017

липса на отговор. Механизмите за липса на отговор или възникване на резистентност са изключително разнообразни. Целта на настоящето проучване е да се опишат морфологични особености, установени при 46 случая с белодробен карцином. Отчетени са хистологичните варианти и подварианти на тумора, имунохистохимична експресия на маркери, като

24 A Chaldakov GN, Aloe L, Tonchev AB, Ghenev P, Maucher A, Fiore M, Zhelezov M. Adipobiology of the brain: from brain diabetes to adipose Alzheimer's disease. Scripta Sci Med 2017

Abstract

Recent studies suggest that diabetes mellitus affects multiple cognitive functions including expression of amyloid precursor protein (APP), amyloid- β (A β) peptide and hyperphosphorylated Tau – molecular signatures of Alzheimer's disease (AD). Further, the administration of streptozotocin (STZ), a well known experimental model for diabetes, induces brain insulin resistance and cognitive alterations resembling those in AD patients. Thus the STZ treatment became a new experimental tool in studying AD, which is increasingly evaluated as type 3 diabetes. Accordingly, the concept of brain diabetes was introduced. We have reported that STZ-induced diabetes is associated with changes in nerve growth factor (NGF) levels in both pancreas and brain (Arch Ital Biol 2007; 145:87-97). Intriguingly, data of an extraneuronal production of both APP and A β peptides including in the adipose tissue were reported. In the last 20 years, adipose tissue and its endocrine secretory proteins (adipokines) take center stage in studying cardiometabolic (including diabetes) and neurodegenerative (including AD) diseases, both associated with adipose-derived neurometabotropic factors (e.g. NGF, BDNF, leptin, adiponectin, betatrophin, neudesin, progranulin, irisin) (World J Pharmacol 2013; 2: 92-99). Altogether, our hypothesis of adipose tissue as a third brain (Obesity Metab 2009; 5: 94-96; Cell Biol Int 2010; 34:1051-1053), herein referred to as adipose AD, may sound more plausible at present. However, the major questions which remain to be answered are: (i) may AD pathology spread from the adipose tissue to the brain, and (ii) may AD be considered a neurometabolic disease.

25 A Ghenev PI, Hinev AI, Evtimov NT, Tunçel N, Panayotov P, Anakievski D, Rančić G, Beltowski J. Multiple faces of adipose tissue. BMR volume 23, p.69 2012

Today, three main types of adipose tissue are recognized: the “classical” brown adipose tissue (BAT) and white adipose tissue (WAT), and the so-called brite adipose tissue (brown-in-white adipose tissue). All these are dynamic multifunctional assemblies composed of adipocytes, fibroblasts, immune cells, nerve bundles, blood vessels, and extracellular matrix. Unlike white adipocytes, which function primarily to store up lipid/energy, brown adipocytes burn lipids to generate heat in a process known as thermogenesis. Recent

26 A Kobakova I, Popov H, Dzhenkov D, Ghenev P. Large lipoma of the colon – a case report and a review of literature. BMR p.78 volume 23, 2012

Lipomas are frequently found benign tumors, originating from the white adipose tissue. They may be with variable size and located at any site in most organs and tissues. In the gastrointestinal tract, large lipomas are rare lesions, most frequently located in the colon and usually reported as incidental findings in 0.3-0.5% of cases in large a
riety of clinical symptoms may be associated with lipomas, depending on their size and location in the gastrointestinal tract (3-5). The most common site for symptomatic solitary lipoma is the ascending colon, including the
transverse colon, including both hepatic and splenic flexures, the descending colon, sigmoid colon and rectum. In the wall of the intestine, most lipomas are located in the submucosal space, less frequently they develop beneath the visceral peritoneal surface. We present here a case of a 60-year-old man

27 A Evtimov NT, Hinev AI, Anakievski D, Zhelezov M, Tonchev AB, Ghenev PI. Adipoparacrinology of prostate cancer. BMR volume 23, 2012; p.96

The global epidemics of obesity and related cardiometabolic, malignant and neurodegenerative diseases has focused attention on adipose tissue biology and the role played by adipose-secreted bioactive molecules (adipokines, neurotrophic factors, fatty acids, prostaglandins, steroid hormones, vitamin D3, NO, H₂S) in the regulation of a wide array of physiological and pathological processes. Until recently, physicians have looked upon obesity as an accumulation of external adipose tissue (subcutaneous and abdominal). This was routinely evaluated by anthropometric measurements including body mass index and waist, hip and, recently, neck circumference.

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