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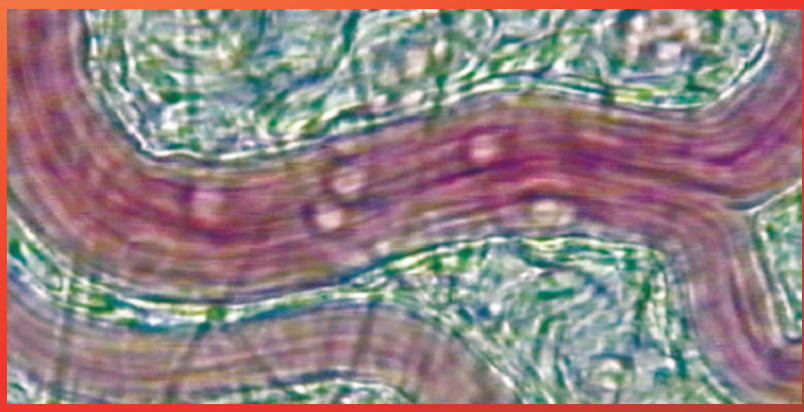

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Sumário / Summary

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EUROPEAN SOCIETY FOR CLINICAL HEMORHEOLOGY
EUROPEAN SOCIETY FOR MICROCIRCULATION

Referência da capa: Vénula pós-capilar (diâmetro aproximado: 30 mm) de rede microvascular em mesentério de rato (*Rattus norvegicus*), observada por microscopia intravital de transiluminação. No interior do vaso sanguíneo visualizam-se leucócitos a interagir com a parede vascular. Imagem obtida por Henrique Sobral do Rosário (Instituto de Biopatologia Química – Prof.ª Doutora Carlota Saldanha, Faculdade de Medicina de Lisboa; Unidade de Biopatologia Vascular, Instituto de Medicina Molecular)

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MICROVESÍCULAS E HEMORREOLOGIA

A existência de microvesículas e de exossomas (microvesículas derivadas dos endossomas) libertados pelas células tumorais é conhecida desde 1970. No entanto, a sua utilização iniciou-se recentemente no diagnóstico não invasivo precoce de alguns tipos de cancro. Marcadores tumorais, tais como as mucinas, podem ser detectados nas microvesículas existentes na urina de portadores de adenocarcinomas. Amostras de sangue de doentes com cancro do ovário revelam mutações no mRNA existente nas microvesículas e nos miRNA específicos contidos nos exossomas associados a esse tipo de cancro.

Para além da proveniência das células tumorais, as microvesículas são também originárias dos componentes corpusculares do sangue e das células endoteliais com funções diversificadas; nomeadamente, participam na comunicação intercelular, na modulação da apoptose e da resposta imune, bem como nos processos da coagulação e angiogénese.

Para além destas interferências nas funções fisiológicas, as microvesículas originam, indirectamente, problemas graves nos doentes que recebem transfusões de sangue armazenado. Um estudo sobre a eficácia das transfusões de sangue armazenado evidenciou que o risco de mortalidade ultrapassa o benefício da transfusão.

A capacidade da hemoglobina libertar oxigénio está diminuída nos eritrócitos do sangue armazenado, o que contribui para a hipoxia tecidual, podendo em alguns casos estar associada à falência multi-órgãos. Durante o armazenamento ocorre a libertação de microvesículas dos eritrócitos, nos quais resultam alterações bioquímicas e hemorreológicas lesivas para a deformabilidade eritrocitária e que, em consequência, afectam a normal oxigenação e a libertação de adenosina trifosfato (ATP).

Em condições normais, o efluxo do ATP pelos eritrócitos induz na célula endotelial a libertação de monóxido de azoto (NO), que é um factor indutor da vasodilatação. No sangue armazenado a forma dos discócitos passa a esferoequinócitos e, após uma transfusão, temos decréscimos da oxigenação tecidual, da vasodilatação e da deformabilidade, a qual contribuirá para o aumento da viscosidade sanguínea e, por consequência, para a diminuição da velocidade do fluxo sanguíneo que favorecerá a manutenção da hipoxia.

Anteriormente à descrição da influência da libertação de microvesículas pelos eritrócitos como causadora das lesões de oxigenação tecidual, já se tinha evidenciado em experimentação animal “in vivo” a formação de microvesículas originárias dos eritrócitos. Durante os 120 dias de meia-vida, o eritrócito vai perdendo microvesículas, o que origina a redução do seu volume. As microvesículas eritrocitárias podem

ser valiosas na transferência de proteínas com âncora glicolipídica (glicosilfosfatidilinositol, GPI) para os eritrócitos de portadores de hemoglobinúria paroxística nocturna (HPN), como demonstrado "in vivo". Na drepanocitose, na alfa-talassemia e na HPN há maior concentração de microvesículas circulantes derivadas dos eritrócitos, relativamente ao estado fisiológico.

No ano passado foi descrito que as microvesículas provenientes dos eritrócitos contêm Factor XI, implicado na iniciação e propagação da acção da trombina. Noutro estudo do mesmo ano foi demonstrado que à superfície das microvesículas contendo fosfatidilserina se pode ligar a Proteína S, que é o cofactor da Proteína C activada; estas duas proteínas, em conjunto, contrariam a acção procoagulante da trombina

Um método simples para separação e caracterização biomolecular de microvesículas provenientes dos eritrócitos foi descrito por nós, com enfoque na utilização do ensino aprendizagem de estudantes de medicina. Noutro estudo, demonstrámos que sondas fluorescentes utilizadas na quantificação do grau de fluidez das membranas eritrocitárias têm a propriedade de induzirem a formação de microvesículas de composição diferente.

No entanto, é necessário o desenvolvimento de métodos que permitam isolar subpopulações de microvesículas de modo homogéneo, para quantificar e analisar "in vivo" as interacções entre os componentes do sangue e a parede do vasos, isto é, inter-relacionar em tempo real os parâmetros hemodinâmicos , a viscosidade sanguínea e as velocidades de cisalhamento. Para melhor compreensão, há a acrescer a necessidade de estudos de simulação, de sinalização química e mecânica, e da proteómica.

Há a salientar que a relevância do tema originou, em 2012, a criação da "International Society for Extracellular Vesicles" com o respectivo órgão difusor, o "Journal of Extracellular Vesicles", e a realização do congresso anual em Boston em 2013.

Desejo a todos Boas Festas e Optimismo para o Novo Ano.

Carlota Saldanha
Presidente da SPHM

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STEM CELL THERAPY IN TRAUMATIC BRAIN INJURY

Nino Muradashvili[1], Richard L. Benton[2], Timothy R. O'Toole[3], Suresh C. Tyagi[1], James B. Hoying[1], David Lominadze[1*]

ABSTRACT

Traumatic brain injury (TBI), which is the most common cause of death and disability after trauma, is accompanied with altered vasculo--neuronal properties due to a variety of inflammatory complications and cognitive dysfunction. Recent studies show that progression of disease may be ameliorated by increased numbers of stem/progenitor cells, which may restore impaired property of neurons and possibly blood vessels and even regenerate them in pericontusional area. The ability of stem cells to self-regenerate and differentiate may contribute to amelioration of physiological dysfunction and possibly cognitive impairments after TBI. The focus of this review is to explore the role and use of stem/progenitor cells in post-TBI healing process.

Key words: Traumatic brain injury, stem/progenitor cells, endothelial progenitor cells, stromal vascular fraction, vasculo-neuronal unit.

TRAUMATIC BRAIN INJURY; VASCULO-NEURONAL UNIT

Traumatic brain injury (TBI) is a devastating public health problem worldwide. It is the leading cause of death and disability after trauma. The harmful effects of TBI occur during primary injury and secondary complications. Primary damage is induced by a mechanical force which results in compression and physical damage of neuro-vascular unit (NVU)[1,2], which consists of cerebral microvessels, glial cells (astroglia, microglia, oligodendroglia), and neurons forming an integrated network that regulates important physiological functions. The secondary complications that may occur hours or days after the injury can be a result of ischemia, inflammation[2,3] and may involve blood- brain barrier (BBB) impairment. BBB is the regulated interface between the peripheral circulation and the central nervous system[3]. Since any vascular or/and blood flow dysfunction, such as regulation of ion balance, homeostasis, changes

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in oxygen and nutrition supply, transport of neurotransmitters and hormones, leads to or/and exacerbates neuronal abnormalities, a term "vasculo-neuronal" dysfunction seems to be more appropriate to define primary source and direction of complications leading to cognitive impairments[3]. However, "neuro--vascular" alterations should define functional impairments originated from damaged neurons and glial cells that affect vasculature.

The treatment of TBI implies active therapeutic approach in the acute phase and the management of long--term posttraumatic complications. The acute care is mostly a complex symptomatic treatment to maintain adequate cerebral perfusion. The aim of long-term therapy is rehabilitation to improve motor function as well as cognitive skills[2]. The main goal of TBI therapy is to achieve the regeneration of damaged vasculo-neuronal unit. Since ability of neurons to repair is very poor, no effective treatment exists other than supportive care, and therefore treatment of TBI still remains a challenge.

Recently, many preclinical and clinical research studies have shown that stem/progenitor cell transplantation has a potential benefits and positive regenerative effects resulting in physiological and functional improvement in many disorders including TBI[4,5].

STEM/PROGENITOR CELLS; NEURONAL STEM CELLS

Commonly used stem/progenitor cells are pluripotent and/or multipotent cells. While pluripotent cells can give rise to most of the cell types that make up the body, multipotent cells can develop into more than one cell type, but this is more limited than that of pluripotent cells. Thus, multipotent cells have an ability of self--renewal and pluripotent cells have the capacity to generate differentiated cells[6-9]. There are two main stem cells types: embryonic stem cells (found in early embryo), and adult (somatic) stem cells. The main sources of somatic stem cells are blood, skin, umbilical cord blood, bone marrow, and adipose tissue.

Neural stem cells (NSCs) are the most commonly used cells in the treatment of neurological disorders including TBI. NSCs are mostly derived from embryonic stem cells[2,6]. It was shown that NSCs were differentiated in neurons and glial cell lines[10]. Treatment of brain injured rats by NSCs showed that these cells may differentiate into neurons and also improve cognitive function[11]. Reduced neurologic deterioration, decreased inflammatory infiltration, and brain edema formation were also reported after NSCs treatment[2].

The majority of research studies is focused on stem cell therapy targeting neuronal regeneration[4] and less is known about their role in vascular repair. Further we will focus on use of stem cells in cerebrovascular repair/regeneration after TBI.

ENDOTHELIAL PROGENITOR CELLS; STROMAL VASCULAR FRACTION

It is known that angiogenesis is crucial for tissue repair and recovery after TBI. Endothelial progenitor

cells (EPCs) have a pivotal role in neovascularization that improves cerebral perfusion and attenuates secondary complications[12]. As a self-defensive mechanism, the number of EPCs is significantly increased in blood 4 days after TBI[13,14]. They migrate toward the injured area and peripheral cerebral tissues to promote neovascularization[12]. Chen et al demonstrated that intravenously administrated spleen-derived EPCs aggregated in the injured area and restored cerebral blood perfusion diminishing the level of brain injury in rats with TBI[12]. Clinical studies also showed that the number of circulated EPCs along with vascular endothelial growth factor (VEGF) and Angiopoetin-1 were increased and positively correlated to Glasgow outcome scale in patients 7 days after severe TBI compared with the healthy controls[14,15]. Park et al showed that bone-marrow derived EPCs treatment had an effect not only on vascular but also on neuronal tissue. Application of EPCs protected secondary post-ischemic axonal and vascular damage in rats after TBI[16]. Comparative studies were done on adipose tissue and bone-marrow derived EPCs[17]. The data showed that both type of EPCs almost equally participated in brain neovascularization and tissue repair. Behavioral improvement was also demonstrated[17].

TBI is accompanied with an increased cerebrovascular permeability to blood proteins caused by impaired endothelial cell properties. We tested the hypothesis that TBI-induced an increase in cerebrovascular permeability can be ameliorated by elevation of EPC numbers. Permeability of pial venules in pericontusional area of mild injury was studied in C57BL/6J mice. After induction of mild TBI, mice were infused with bone marrow-derived EPCs in 100 ml of phosphate buffered saline (PBS) or with PBS alone (control group) through an external jugular vein. After 14 days, pial venular permeability was assessed in these mice by measuring the extravascular accumulation of fluorescein isothiocyanate-labeled bovine serum albumin using an intravital fluorescence microscope. Cerebrovascular leakage was decreased in mice infused EPCs compared to that in mice infused with PBS alone. These results suggest that TBI-induced increased cerebrovascular permeability can be ameliorated by enhancing the number of EPCs, which can restore impaired property of vascular endothelium in pericontusional area[18].

Adipose tissue is a very abundant source of mesenchymal stem cells and surgically easily accessible [19]. The stromal vascular fraction (SVF) from adipose tissue is very heterogeneous cell isolate and a rich source of regenerative cells, including mesenchymal stem cells[19]. SVF also contains endothelial, smooth muscle, blood, and other stromal/mesenchymal cells[19,20]. Used either as an allogeneic or autologous preparation, SVF cell therapy has a complex healing effect on the vasculature. LeBlanc et al demonstrated that treatment with the SVF after an acute myocardial infarction caused increased microvascular perfusion in the peri-infarct area and improved functional flow reserve, even without changing microvessel density, resulting in ameliorated cardiac dysfunction post-MI[19]. So far, there are no studies

published on the effect of SVF after TBI. Our preliminary data showed that macromolecular permeability was lessened in mice infused with SVF compared to that in mice infused with PBS alone (unpublished data).

CONCLUSION

Presently treatment of TBI is challenging and mainly is based on repair of damaged NVU. While this approach seems promising, targeting vasculo-neuronal unit in anticipation of improvement of overall brain function should also be used. Stem/progenitor cell therapy is the most promising treatment in post-TBI based on their ability of self-regeneration and differentiation. Similarly, transplantation of SVFs has a great potential because of their homologues affinity. However, mechanisms of stem cells proliferation, regeneration, survival and function must be fully understood to be freely used in the future in post--TBI treatment.

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MICROCIRCULATION IN HYPERTENSIVE PATIENTS

Jung F[1], Pindur G2, Ohlmann P3, Spitzer G4, Sternitzky R4, Franke RP5, Leithäuser B6, Wolf S7, Park JW8

Abstract

Regardless of the mechanisms that initiate the increase in blood pressure, functional and structural changes in the systemic vasculature are the final result of long-standing hypertension. These changes can occur in the macro- but also in the microvasculature. The supply of the tissues with oxygen, nutrients, and metabolites occurs almost exclusively in the microcirculation (which comprises resistance arterioles, capillaries and venules), and an adequate perfusion via the microcirculatory network is essential for the integrity of tissue and organ function. This review focuses on results from clinical studies in hypertensive patients, which have been performed in close cooperation with different clinical groups over the last three decades. Intravital microscopy was used to study skin microcirculation, microcatheters for the analysis of skeletal muscle microcirculation, the slit lamp for conjunctival microcirculation and the laser scanning ophthalmoscope for the measurement of the retinal capillary network. The first changes of the normal microcirculation can be found in about 93% of patients with essential hypertension, long before organ dysfunctions become clinically manifest. The earliest disorders were found in skin capillaries and thereafter in the retina and the skeletal muscle. In general, the disorders in the different areas were clearly correlated. While capillary rarefaction occurred mainly in the retina and the conjunctiva bulbi, in skin capillaries morphological changes were rare. A significant decrease of capillary erythrocyte velocities under resting conditions together with a marked damping of the postischemic hyperemia was found, both correlating with the duration of hypertension or WHO stage or the fundus hypertonicus stage. Also the mean oxygen tension in the skeletal muscle was correlated with the state of the disease. These data show that the microcirculatory disorders in hypertension are systemic and are hallmarks of the long-term complications of hypertension. There is now a large body of evidence that microvascular changes occur very early and may be important in their pathogenesis and progression.**[Biorheology. 2013;50(5-6):241-55. doi: 10.3233/BIR-130645] PMID:24398607**

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CARDIOVASCULAR BENEFITS OF PHLEBOTOMY: RELATIONSHIP TO CHANGES IN HEMORHEOLOGICAL VARIABLES

Holsworth RE Jr[1], Cho YI, Weidman JJ, Sloop GD, St Cyr JA

Abstract

Renewed interest in the age-old concept of "bloodletting", a therapeutic approach practiced until as recently as the 19th century, has been stimulated by the knowledge that blood loss, such as following regular donation, is associated with significant reductions in key hemorheological variables, including whole blood viscosity (WBV), plasma viscosity, hematocrit and fibrinogen. An elevated WBV appears to be both a strong predictor of cardiovascular disease and an important factor in the development of atherosclerosis. Elevated WBV through wall shear stress is the most direct physiological parameter that influences the rupture and erosion of vulnerable plaques. In addition to WBV reduction, phlebotomy may reduce an individual's cardiovascular risk through reductions in excessive iron, oxidative stress and inflammation. Reflecting these findings, blood donation in males has shown significant drops in the incidence of cardiovascular events, as well as in procedures such as percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. Collectively, the available data on the benefits of therapeutic phlebotomy point to the importance of monitoring WBV as part of a cardiovascular risk factor, along with other risk-modifying measures, whenever an increased cardiovascular risk is detected. The development of a scanning capillary tube viscometer allows the measurement of WBV in a clinical setting, which can prove to be valuable in providing an early warning sign of an increased risk of cardiovascular disease. **[Perfusion. 2014 Mar;29(2):102-16. doi: 10.1177/0267659113505637]. PMID:24045034**

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OXIDATIVE STRESS AND SUICIDAL ERYTHROCYTE DEATH

Lang F[1] Abed M, Lang E, Föller M

Abstract

Eryptosis, the suicidal erythrocyte death, is characterized by cell shrinkage, membrane blebbing, and phosphatidylserine translocation to the outer membrane leaflet. Phosphatidylserine at the erythrocyte surface binds endothelial CXCL16/SR-PSOX (CXC-Motiv-Chemokin-16/Scavenger-receptor-for-phosphatidylserine-and-oxidized-low-density-lipoprotein) and fosters engulfment of affected erythrocytes by phagocytosing cells. Eryptosis serves to eliminate infected or defective erythrocytes, but excessive eryptosis may lead to anemia and may interfere with microcirculation. Clinical conditions with excessive eryptosis include diabetes, chronic renal failure, hemolytic uremic syndrome, sepsis, malaria, iron deficiency, sickle cell anemia, thalassemia, glucose 6-phosphate dehydrogenase deficiency, glutamate cysteine ligase modulator deficiency, and Wilson's disease.

Recent advances

Eryptosis is triggered by a wide variety of xenobiotics and other injuries such as oxidative stress. Signaling of eryptosis includes prostaglandin E_2 formation with subsequent activation of Ca(2+)-permeable cation channels, Ca(2+) entry, activation of Ca(2+)-sensitive K(+) channels, and cell membrane scrambling, as well as phospholipase A2 stimulation with release of platelet-activating factor, sphingomyelinase activation, and ceramide formation. Eryptosis may involve stimulation of caspases and calpain with subsequent degradation of the cytoskeleton. It is regulated by AMP-activated kinase, cGMP-dependent protein kinase, Janus-activated kinase 3, casein kinase 1α, p38 kinase, and p21-activated kinase 2. It is inhibited by erythropoietin, antioxidants, and further small molecules.

Critical issues

It remains uncertain for most disorders whether eryptosis is rather beneficial because it precedes and thus prevents hemolysis or whether it is harmful because of induction of anemia and impairment of microcirculation.

Future directions

This will address the significance of eryptosis, further mechanisms underlying eryptosis, and additional pharmacological tools fostering or inhibiting eryptosis. **[Antioxid Redox Signal. 2014 Jul 1;21(1):138-53. doi: 10.1089/ars.2013.5747]. PMID:24359125**

[1] Department of Physiology, University of Tübingen, Tübingen, Germany.

ELEIÇÕES PARA ÓRGÃOS SOCIAIS DA SPHM

No dia 17 de Novembro de 2014 decorreram, em Assembleia Geral, as eleições para os Órgãos Sociais da Sociedade Portuguesa de Hemorreologia e Microcirculação, biénio de 2014-2016.

Após se ter procedido à contagem dos votos, comprovou-se que a única lista concorrente foi aprovada por unanimidade, tendo sido apurados os seguintes resultados: 15 votos a favor, zero votos brancos e zero votos nulos.

A lista eleita é constituída pelos seguintes membros:

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Delegado da Região Sul e Regiões Autónomas: Dr. Mário Marques

PARTICIPAÇÃO NACIONAL EM CONGRESSOS DE HEMORREOLOGIA E MICROCIRCULAÇÃO

(1) Workshop **"Repercussions in eye microcirculation of patients with systemic vascular disease"**, que ocorreu no 4th International Conference on Clinical & Experimental Ophthalmology July 14-16 July Baltimore, USA, foi organizado por Carlota Saldanha e Paulo Leal Filipe. A Fundação Luso- Americana patrocinou parte da participação de Carlota Saldanha.

Abstract:

"Repercussions in eye microcirculation of patients with systemic vascular disease"
Paulo Filipe & Carlota Saldanha

Associations between systemic vascular disease parameters and their repercussions in ocular blood flow velocities which will be analysed

There is an important link between skin and eye not always perceptive to dermatologists and ophtalmologists, much less the fact that many cutaneous diseases course with ocular manifestations. These may range from the relatively frequent diseases such as acne rosacea, allergic diseases like contact eczema and atopic dermatitis with its associated chronic eye lid and conjunctival inflammation, to the profoundly vision-threatening ocular consequences of ichthyoses, pemphigoid, Stevens Johnson syndrome, pseudoxanthoma elasticum, infectious conditions including ophthalmic herpes zoster and periorbital cellulitis. Even some types of skin cancer may involve the eyelid. Moreover, some drugs used in Dermatology namely antimalarials, corticosteroids and photosensitizers, may induce ocular adverse events implicating ophthalmologic examination on a regular basis.

(2) Comunicação do trabalho **"Fibrinogen effects on erythrocyte nitric oxide mobilization in presence of timolol"**, apresentado por Carlota Saldanha no Workshop Ocular Microbiology/ Immunology", do 4th International Conference on Clinical & Experimental Ophthalmology, July 14-16 July Baltimore, USA. A Fundação Luso-Americana patrocinou parte da participação de Carlota Saldanha.

Abstract:

"Fibrinogen effects on erythrocyte nitric oxide mobilization in presence of timolol"

C Saldanha, R Esteves, L Zabala, T Freitas, P Teixeira, P Napoleão, Ana S Silva-Herdade*

*Institute of Biochemistry, Institute of Molecular Medicine, Faculty of Medicine University of Lisbon

Aims: The objectives of this study were to evaluate the effects of high fibrinogen concentration on erythrocyte mobilization of nitric oxide (NO) and of its metabolites in presence of timolol in healthy human blood samples.

Main Methods: Levels of NO was evaluated by amperometric method. Nitrite, nitrate and S-nitrosoglutathione (GSNO) were measured using the spectrophotometric Griess reaction.

Key findings: In the presence of high concentrations of fibrinogen and timolol (10μM) in the blood samples from healthy humans the erythrocyte nitrites, nitrates and GSNO concentration increased without significant changes in NO efflux. Erythrocyte scavenging NO property was preserved in the presence of timolol and high fibrinogen levels.

Significance: These results suggest that during in inflammation when high levels of fibrinogen are present, NO delivery by erythrocytes might be compromised that acts as a compensatory mechanism against the overproduced NO by endothelial inducible nitric oxide synthase.

Keywords: erythrocyte nitric oxide, S-nitrosogluthatione, fibrinogen

(3) O trabalho **"Fibrinogen signalling in erythrocyte nitric oxid mobilization in presence of PI3-K and adenylyl cyclase inhibitors"** foi apresentado no XXIIIrd International Fibrinogen Workshop 9-11 July 2014, Marseille, France, por Carlota Saldanha. Esta participação teve o apoio da Fundação para a Ciência e Tecnologia.

Abstract:

Fibrinogen Signalling in Erythrocyte Nitric Oxide Mobilization in Presence of PI3-K and Adenylyl Cyclase Inhibitors.

Saldanha C, Freitas T, Herdade AS., Lopes de Almeida JP

Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa

carlotasaldanha@fm.ul.pt

Fibrinogen is a plasma protein that beyond its hemostatic function behaves as an acute phase protein and as a hemorheological factor. The erythrocyte hyperaggregation state induced by fibrinogen occurs in various metabolic and vascular diseases Soluble form of fibrinogen binds to erythrocyte CD47. Soluble thrombospondine binds erythrocyte CD47 in a sequence peptide known as 4N1K. Fibrinogen reinforces the ability of erythrocyte to scavenger nitric oxide (NO).

However hiperfibrinogenemia induced in vitro increased erythrocyte NO efflux in dependence of band 3 phosphorylation degree. When in presence of the CD47 agonist peptide, 4N1K, and at hiperfibrinogenemia a variation was observed in erythrocyte NO mobilization.

The aim of this work was to study the effect of fibrinogen, on the erythrocyte NO mobilization under influence of PI3-K and adenylate cyclase inhibitors in absence and presence of CD47 agonist peptide, 4N1K

In this in-vitro study, whole blood samples were harvested from healthy subjects and NO, peroxynitrite, nitrite, nitrate and S-nitroglutathione (GSNO) were determined in presence of 4N1K, wortmannin (PI3-K inhibitor), MDL (adenylyl inhibitor) and under high fibrinogen concentrations. The results obtained, when 4N1K is present with wortmannin in presence of high fibrinogen levels show, in relation to control, (1) no variations on the levels the erythrocyte NO efflux; (2) increased concentrations of nitrite ($p<0.0001$) and nitrate ($p<0.0001$)and GSNO concentrations ($p<0.001$. Regarding the values peroxynitrite they are decreased ($p<0.005$), both to control to samples with fibrinogen plus wortmannin

The results obtained, when 4N1K is present MDL in presence of high fibrinogen levels show, in relation to control, (1) no variations on the levels the erythrocyte NO efflux; (2) increased concentrations of nitrite ($p<0.001$) and nitrate ($p<0.001$) and GSNO concentrations ($p<0,001$). Regarding the values of GSNO they are increased ($p<0.005$) in relation to samples with MDL plus fibrinogen.

In conclusion, under fibrinogen stimulus, the presence of 4N1K peptide reinforce in the erythrocyte GSNO, nitrite and nitrate levels, decreasing peroxynitrite concentration and preserving their scavenger NO ability in absence and presence of PI3K inhibitor.

Under fibrinogen stimulus, the presence of 4N1K peptide reinforce in erythrocyte the efflux of NO, GSNO,nitrite and nitrate levels in presence of the adenylyl cyclase inhibitor.Lower levels of cAMP favours in erythrocyte the efflux of NO under fibrinogen, 4N1K and MDL stimuli.

In conclusion fibrinogen induces erythrocyte NO mobilization independent of PI3-K and adenylate cyclase inhibitors that is unchanged by the presence CD47 agonist peptide, 4N1K.

The ability of erythrocyte to scavenger NO is not changed by PI3-K or adenylate cyclase even in absence or presence of 4N1K.

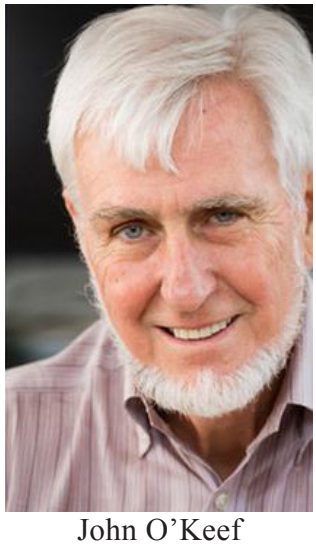
PRÉMIO NOBEL DE MEDICINA/2014

The Nobel Assembly at Karolisnska Institutae, por comunicação divulgada no dia 6 de Outubro passado, decidiu atribuir aos neurocientistas John O'Keef, May-Britt Moser e Edward Moser o Prémio Nobel em Medicina de 2014, pelos trabalhos que desenvolveram em células nervosas intervenientes na orientação espacial cerebral. Metade do valor do prémio foi concedida a John O' Keef, sendo a restante partilhada pelo casal May-Britt Moser e Edward Moser.

John O'Keef (natural de Nova Iorque, 1939) é professor em Institute of Cognitive Neuroscience, Department of Anatomy, University College London. May Britt Moser (natural de Fosnavåg, 1963), psicóloga, fundou e dirige o Kavli Institute for Systems Neuroscience and Centre for the Biology of Memory, Norwegian University of Science and Technology, Trondheim. Edward Ingjald Moser (natural de Ålesund, 1962) é psicólogo, neurocientista e director do Kavli Institute for Systems Neuroscience and Centre for Neural Computation, Norwegian University of Science and Technology.

John O'Keef identificou os primeiros componentes daquele sistema de orientação cerebral no hipocampo de ratos, em 1971. Através dos sinais eléctricos gerados por células individualizadas, verificou que determinadas células "denominadas "células de lugar", estavam activas quando se encontravam em determinado posicionamento na região.

Por seu lado, May-Britt (natural de e Edward Moser descobriram, em 2005, que células do córtex entorrinal (adjacente ao hipocampo), eram activadas quando os ratos passavam rapidamente por determinados locais dispostos em grelha hexagonal. Concluíram que as "células de lugar" actuavam em conjunto com as de "grelha", constituindo um sistema cerebral de posicionamento espacial. Admite-se que estes resultados possam explicar os sintomas iniciais da doença de Alzheimer, atribuídos a lesões celulares precoces no córtex entorrinal.


John O'Keef


May-Britt Moser


Edward Ingjald Moser

PRÓXIMAS REUNIÕES INTERNACIONAIS

4th Micro and Nano Flows Conference, MNF2014
September 7-10, 2014, University College London

15th International Congress of Biorheology and 8th International Conference on Clinical Hemorheology
May 24-28, 2015, Seoul, Korea
Please visit the official web site for this conference at http://isb-isch2015.org for further details.

18th European Conference on Clinical Hemorheology and Microcirculation

Lisboa vai receber, em 2016, a 18th European Conference on Clinical Hemorheology and Microcirculation. O evento será organizado pela Sociedade Portuguesa de Hemorreologia e Microcirculação.

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OUTRAS INFORMAÇÕES

Perspectivas da Hemorreologia na Wikipedia
http://en.wikipedia.org/wiki/Hemorheology

Clinical Hemorheology and Microcirculation
Jornal oficial das Sociedades Científicas de Hemorreologia
http://www.iospress.nl/journal/clinical-hemorheology-and-microcirculation/

REGRAS DE PUBLICAÇÃO / INSTRUCTIONS TO AUTHORS

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A Sociedade Portuguesa de Hemorreologia e Microcirculação (SPHM) aceita para publicação no seu BOLETIM artigos de curta extensão. O Boletim é editado quatro vezes por ano em formato de papel e electrónico (www.hemorreologia.com), sendo distribuído gratuitamente a individualidades e instituições científicas e culturais.

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(Extensão máxima do texto: 5 a 6 páginas a um espaço (letra de corpo 11), incluindo figuras tabelas e quadros(e respectivas legendas),agradecimentos e até 30 referências bibliográficas).

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INVITATION

The Portuguese Society on Hemorheology and Microcirculation (Sociedade Portuguesa de Hemorreologia e Microcirculação, SPHM) is pleased to welcome short papers for publication in its BOLETIM. This publication, in paper and online (www.hemorreologia.com), is distributed four times a year free of charge to the members of the Society.

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