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Sumário / Summary

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EUROPEAN SOCIETY FOR CLINICAL HEMORHEOLOGY
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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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MICROSCOPIA INTRAVITAL E HEMORREOLOGIA

Vamos associar duas palavras-chave de cariz diferente, uma essencialmente técnica e outra um nicho científico amplo, que abrange a biofísica, a bioquímica e a biomecânica. Naturalmente interrogamo-nos sobre o porquê e, penso que o motivo pode ser justificado pela frase "*The most pervasive fallacy of philosophic thinking goes back to neglect of context*", de John Dewey (1859-1952), americano filósofo, psicólogo e pedagogo.

Essa ligação, que não pretende ser exaustiva de todo, vai ser focada a nível da microcirculação constituída pela rede capilar, arteríolas e vénulas, e com funções de regulação do fluxo sanguíneo nos órgãos e das trocas moleculares entre tecidos e o sangue. As arteríolas possuem mecanismos sensoriais que monitorizam a tensão de cisalhamento e a tensão circunferencial. Estamos a falar de sensores nas membranas endoteliais que respondem à tensão de cisalhamento e que enviam mensagens moleculares aos mecanismos contrácteis nos vasos. A transmissão é influenciada pelas propriedades reológicas do sangue, por alterações crónicas das forças de cisalhamento, pelos danos de provocados nos vasos que induzem à presença de factores pro-inflamatórios e ao desequilíbrio da hemostase.

A microscopia intra-vital (IVM) permite, no contexto próprio e aplicada a modelos experimentais *in vivo*, acrescer para a clarificação, das relações moleculares intraluminais e teciduais. Por exemplo, nos modelos de trombose arterial em murganhos normais ou deficientes em proteínas participantes nas vias da coagulação conseguiu observar-se o contributo das microvesículas derivadas dos monocitos na formação do trombo[1,2]. Pela observação das vénulas sinusóides e das pós-sinusóides por IVM, verificou-se num modelo experimental de endotoxemia em murganhos que a adesão dos leucócitos é posterior à das plaquetas[3]. O nosso grupo reportou que a fluoresceina sódica, normalmente utilizada na clínica para observação da microcirculação coroideo-retiniana, induziu uma resposta inflamatória mediada pelo aumento do recrutamento de leucócitos à célula endotelial das vénulas pós-capilares do mesentério de ratos, observado por IVM[4]. Previamente, tínhamos demonstrado, num modelo de isquémia e reperfusão e utilizando IVM para observação da microcirculação no mesentério, que o número de leucócitos em rolamento e ou aderentes aumentou após a reperfusão nos ratos submetidos a isquemia bilateral dos membros posteriores[5]. A retenção de leucócitos na microcirculação do mesentério é exacerbada pela presença de velnacrina maleato, um dos inibidores da acetilcolinesterase, num modelo experimental de endotoxemia induzida em ratos Wistar[6]. A observação por IVM das inte-

racções leucócito-parede endotelial em vénulas pós-capilares forneceu parâmetros hemodinâmicos que, em conjunto com os valores da viscosidade sanguínea determinados a várias velocidades de cisalhamento e hematócritos diferentes, permitiram por simulação matemática identificar na superfície dos leucócitos próxima da célula endotelial uma distribuição não uniforme de tensões de cisalhamento[7]. A zona de maior tensão de cisalhamento localizava-se na superfície próxima da célula endotelial, formando como que um duplo gradiente em que as de menor intensidade se estabeleciam nas zonas distais[7]. Foi também calculado que o comportamento hidrodinâmico de agrupamentos de leucócitos é indutor da iniciação e potenciação do rolamento e do aumento da tensão de cisalhamento na parede endotelial[7,8]. O leucócito, ao ser recrutado, é auxiliado pelo movimento lateral próprio, pela ocorrência de vórtices e de regiões de fluxo estagnadas que o envolvem[9]. Ao chamamento quimiotáctico juntam-se o ambiente hidrodinâmico, o biomecânico e os empurrões resultantes das interacções que estabelecem com os eritrocitos, constituindo um conjunto de condições propícias ao recrutamento dos leucócitos para a célula endotelial[10]. Diferentes autores utilizaram a marcação fluorescente dos glóbulos vermelhos de ratos Wistar para avaliar, por IVM, os efeitos de várias moléculas tais como a endotelina-1 e ou a endotoxina na microcirculação hepática[11,12]. Concluíram que a velocidade do fluxo sanguíneo na microcirculação hepática varia consoante a dose administrada de endotoxina[11]. O estudo com a endotelina[12] permitiu elaborar um método de quantificação da heterogeneidade da microcirculação entre e dentro dos lóbulos hepáticos induzida pelo stress.

O efeito da acetilcolina no fluxo sanguíneo na microcirculção, após a formação de novos capilares no córtex cerebral, foi também avaliado por IVM, que mostrou aumento da velocidade dos eritrocitos e maior capacidade de relaxamento vascular nos murganhos previamente injectados com factor de crescimento derivado das plaquetas[13].

A microscopia intravital é uma "ferramenta "essencial para a compreensão do comportamento biomolecular, com propriedades bioquímicas, biofísicas, biomecânicas, a nível da microcirculação *in vivo*, e será tanto mais valorativa quanto mais aperfeiçoada estiver a análise computacional dos dados.

Carlota Saldanha
Presidente da SPHM

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THE AUTODIGESTION HYPOTHESIS IN SHOCK AND MULTI-ORGAN FAILURE: DEGRADING PROTEASE ACTIVITY

Geert W. Schmid-Schönbein Ph.D., Alex Penn Ph.D., and Erik Kistler M.D. Ph.D.[1]

ABSTRACT

Shock and multi-organ failure have one of the highest levels of inflammatory markers, morbidities and mortality. The underlying mechanisms are currently unknown and no effective intervention exists. We present evidence for a previously untested mechanism due to *autodigestion* by the digestive enzymes synthesized in the pancreas and transported in the lumen of the intestine as normal part of food digestion. We summarize experimental evidence in support of the autodigestion hypothesis and a new approach for possible intervention against multi-organ failure that is currently entering clinical trials.

Key-words: Intestine; digestive pancreas; inflammation; trypsin; chymotrypsin; elastase; intestinal mucosa; hemorrhagic shock; sepsis.

INTRODUCTION

Multi-organ failure after shock, with its high mortality, is one of the most important clinical problems. No mechanism has yet been proposed that enjoys universal acceptance. We present here a new proposal for the rapid organ failure in shock that is linked to the digestive system.

To introduce the idea we consider the following question: What mechanisms allow digestion of a meal, even ingested intestine, while preventing digestion of one's own intestinal tissue? Why does our intestine not digest itself? Nature had to find a solution to this problem long before humans or other mammals walked the earth, and thus any protection mechanism against autodigestion is likely developmentally old and of course robust. That does not imply that the protection is limitless. We

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propose here that failure to protect against autodigestion by our own digestive enzymes may be a cause for multi-organ failure.

A Common Denominator in Human Diseases

In the past decades a large body of clinical evidence has brought to light evidence supporting the idea that the majority of human diseases are accompanied by significantly elevated levels of markers for inflammation (Ballantyne and Nambi, 2005; Blake and Ridker, 2001; Claus *et al.*, 2010). This evidence follows previous decades of experimental and smaller clinical studies analyzing many details of the inflammatory cascade (Zweifach *et al.*, 1974). The analysis brings to light that preclinical and clinical evidence is in agreement about a role of inflammation in human disease. Inflammation has moved into the center of research in many branches of medicine, from hypertension, diabetes, atherosclerosis, stroke, cardiac infarction, renal failure, chronic degenerative diseases, to cancer, to name just a few.

This development raises important questions about the significance of the inflammatory cascade in disease. Why would such a diversity of diseases in different organs utilize common biochemical and biophysical pathway? What mechanisms and pathways stimulate an inflammation?

Inflammation as requirement For tissue repair

The inflammatory cascade serves a lifetime for wound healing and tissue repair. The ability to repair is quite evident when we consider a small tissue injury, e.g. a cut into the skin. Following the initial injury, there is a stereotypic cascade of events that at the cellular level starts with:

- cell activation in the form of a transmembrane ion exchange and spontaneous degranulation by multiple cell types;
- breakdown of cell membrane adhesion mechanisms, e.g. elevated permeability of the vascular and lymphatic endothelium and other cell layers;
- expression of membrane adhesion molecules to facilitate binding of circulating cell to the endothelium including a specific sequence of steps for leukocyte adhesion that is highly cell-type specific;
- migration and differentiation of cells into the injured tissue;
- removal of injured cells and extracellular matrix fragments by apoptosis or necrotic phagocytosis;
- to the eventual generation of new tissues by local mitosis with growth factors and by infiltration and differentiation of stem cells.

At the end of this cascade is *resolution of inflammation* in the form of a new scar tissue that may or may not have the same structure and function as the injured tissue that it replaces (Carlo and Levy, 2010; Gonzalez--Periz and Claria, 2010; Gronert, 2010; Lawrence and Fong, 2010; Soehnlein and Lindbom, 2010). The repair process requires days and weeks and is repeated many times in life. According to our current understanding it is the *only repair* mecha-

nism in living tissues (Schmid-Schönbein, 2006).

Thus, if one looks at inflammatory makers as a sign of the repair mechanism in action, the immediate question arises for many diseases: What event caused injury to the tissue in the first place and triggered the inflammatory repair cascade? We have a keen interest to answer this important question, since it may serve as the key to preventive measures. In the following we will investigate these questions for the case of shock and multi-organ failure.

Tissue Injury in Shock

In physiological shock many injury mechanisms have been proposed, e.g. infections (viral, bacterial, fungal), trauma, exposure to elevated or reduced mechanical stress, extreme temperatures, and chemical exposures to name a few. Depletion of anti-inflammatory pathways may also trigger an inflammation.

However, it is also evident that other mechanisms exist. For example in hemorrhagic and in several forms of septic shock, severe inflammation can be rapidly generated in the absence of any of the tissue injury mechanisms listed above. Anti-biotic treatment has so far been largely ineffective in clinical trials of septic patients and so have been interventions against mediators derived from infection (e.g. endotoxin) or against some inflammatory mediators/markers (e.g. TNFα, Il-1, complement) (Brierre *et al.*, 2004; Derkx *et al.*, 1999; Harlan and Winn, 2002; Kalil and Sun, 2011; Kumar *et al.*, 2010; Solomkin, 1994; Zanotti and Kumar, 2002; Ziegler, 1988). The lack of positive outcomes of clinical trials suggests that even though these markers of inflammation may be present in shock plasma, they themselves may not be the cause for the tissue injury in shock.

Shock and Multi-Organ Failure: Plasma-Derived Mediators

It is useful to look more in detail into the properties of the plasma that one can collect in shock. Shock plasma (and also lymphatic fluid derived from the intestine) contains numerous inflammatory mediators. In hemorrhagic shock for example, the earliest signs of inflammation in the form of enhanced circulating leukocyte activation can already be detected within minutes after reduction of central blood pressure (Barroso-Aranda *et al.*, 1995). It is apparent that there is early proinflammatory signal generation that does not require de novo gene expression. Within one hour this cell activation reaches levels that can help to discriminate between survivors and non-survivors (Barroso-Aranda and Schmid-Schönbein, 1989).

The plasma of animals in shock exhibits a diversity of activities, e.g. it activates naive donor leukocytes and at the same time depresses many normal cell functions. In the case of the heart muscle this property has been designated as *myocardial depressing factor* (Lefer, 1974).

A number of candidate mediators have been proposed to explain the proinflammatory activity in the plasma, e.g. endotoxin, complement cascade products, cytokines, arachado-

nic acid products, to name a few. Depletion of anti-inflammatory mediators has also been suggested (e.g. IL-10, glucocorticoids).

Decades of research have not led to identification of a unique chemical entity responsible for the proinflammatory activity in plasma of shock animals or humans. Instead we propose here a new approach to this important problem.

The Pancreatic Enzymes in Inflammation

The idea is as follows: If early during hemorrhagic shock (when only blood volume is reduced and no agents or drugs were administered) inflammatory mediators are detected then the implication is that these mediators must be pre-formed or otherwise rapidly produced, rather than synthesized de novo. Analysis of homogenates from different tissues in the rat shows that the *pancreas* – but less so other organs – is able to generate in a short period of time (minutes) powerful proinflammatory (in form of leukocyte activation) and even cytotoxic mediators (Kistler *et al.*, 2000a). The intestine is also able to do so, but only if pancreatic digestive enzymes are present (Penn *et al.*, 2007). In the absence of pancreatic digestive enzymes in the lumen of the intestine, intestinal homogenates produce low levels of inflammation. Similarly, other organ homogenates (heart, brain, liver, kidney and others) induce low levels of inflammation, but they are equally inflammatory or cytotoxic if mixed with pancreatic digestive enzymes (Penn *et al.*, 2007; Waldo *et al.*, 2003). This evidence implicates *pancreatic digestive enzymes* as key players in the formation of a pro-inflammatory mediator in plasma already during early periods of hemorrhagic shock.

Pancreatic enzymes are also implicated in the production of myocardial depressant factor, which is thought to be a proteolytically derived peptide of pancreatic origin (Lefer and Glenn, 1971). Direct test of the pancreatic homogenates shows that they activate neutrophils and simultaneously depress myocardial contraction (Kistler *et al.*, 2000b). Inflammation generated by pancreatic homogenates can largely be recreated by incubating previously non-inflammatory tissues with pancreatic enzymes such as trypsin and chymotrypsin.

The activity generated by the pancreas is largely derived from lower molecular weight constituent (<10 kD), implicating cleaved pancreatic peptides as inflammatory mediators (Kistler *et al.*, 2000b). In addition, free fatty acids formed in the autodigestion process have been implicated in inflammation generated by pancreatic homogenates. Systemic circulatory effects of the homogenates appear to be largely peptide related, while fatty acid production may account for a large proportion of white blood cell activation and direct cytotoxicity (Kramp *et al.*, 2003; Penn and Schmid-Schönbein, 2008; Waldo *et al.*, 2003).

Digestive Enzymes in the Intestine: What prevents Autodigestion?

The role of pancreatic enzymes within the lumen of the intestine is in agreement with many studies that

have recognized the special role of the intestine during shock (Chang, 1997). As part of its fundamental role in digestion, the intestine is the only organ that normally receives pancreatic digestive enzymes into its lumen. Under normal physiologic conditions, pancreatic digestive enzymes are activated by enterokinases in the intestinal lumen and digest most biological polymers into their monomeric constituents, thus facilitating transport across the mucosal barrier.

Thus we return to the question: What mechanisms prevent digestion of one's own intestine when such powerful digestive enzymes are present and activated? Current evidence points to the mucosal epithelial barrier as the predominant mechanism that serves to compartmentalize the digestive enzymes in the lumen of the intestine. Under normal physiological conditions intestinal permeability is low enough to prevent escape of digestive enzymes from the bowel lumen into the intestinal wall (including smaller proteases, such as trypsin (~19K Da). Circulating plasma protease inhibitors (e.g. serpins) act as a second buffer against intestinal protease leakage and deleterious systemic proteolytic activation (e.g. leukocyte elastase).

Entry of Digestive Enzymes into the Ischemic Intestinal Wall

The selective barrier properties of the mucosal epithelium depend on mucin secretion (Qin et al., 2010) and on the tight junctions between epithelial cells covering the villi (Perry et al., 1999). This barrier is essential to prevent entry of digestive enzymes into the intestinal wall. As a biological barrier it is, however, sensitive to many influences, including oxygen depletion, the presence of inflammatory mediators, the intestinal bacteria, and passage of partially digested food items.

In hemorrhagic shock the intestinal perfusion and oxygen levels are reduced. This process is sufficient to enhance the permeability of the mucosal barrier by opening the tight junctions between epithelial cells (Rollwagen et al., 2000) and allowing pancreatic digestive enzymes, like trypsin, access into the wall of the intestine. The digestive enzyme are transported into the villi and the smooth muscle layer, and even across the outermost collagen sheet of the intestine (serosa) into the peritoneum (Ishimaru *et al.*, 2004; Rosario *et al.*, 2004).

Pancreatic enzyme leakage into the intestinal wall is a truly catastrophic event for the structure and function of the intestine since there is little inhibition of digestive protease once inside the wall of the intestine. The intestinal villi are subject to enzymatic digestion and rapidly lose their morphological structure, the digested tissue detaches from the intestine to the point of complete cleavage of the villi down to their bases. This mucosal barrier and tissue destruction provides the digestive enzymes unimpeded access into the intestinal wall (Fig. 1) (Fitzal *et al.*, 2002; Mitsuoka *et al.*, 2000).

With the ensuing injury, the intestinal tissue and Peyer's patches swell and exhibit hemorrhage into the interstitial tissue, a sign of blood vessel wall destruction in the intestinal microvasculature. All interstitial struc-

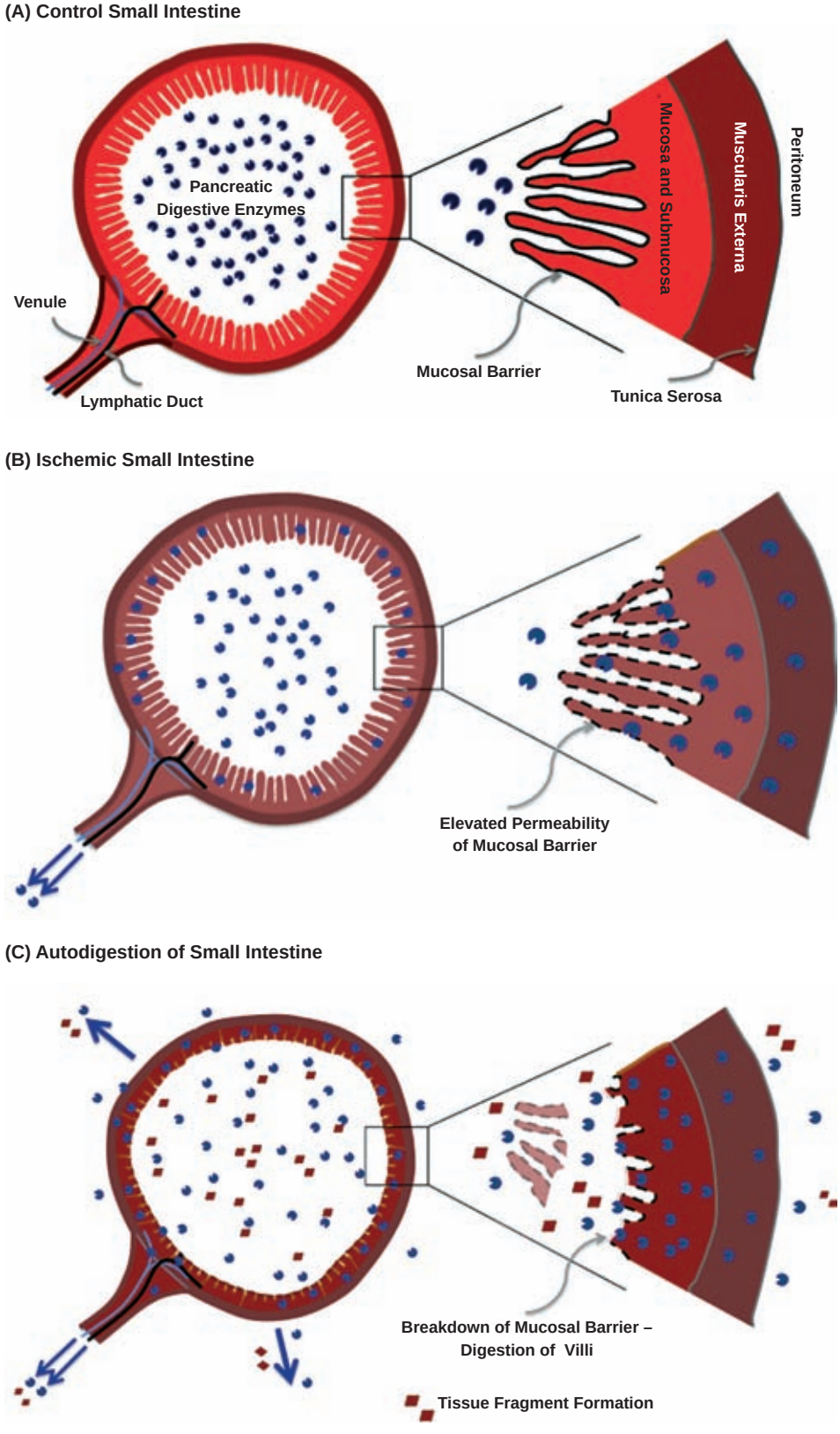

Fig. 1 – Schematic diagram of pancreatic digestive enzyme transport in the small intestine. (Panel A) Compartmentalization of digestive enzymes inside the lumen of a normal intestine by the mucosal barrier with minimal transport into the intestinal wall; (B) escape of digestive enzymes into the wall of an ischemic intestine after elevation of the mucosal barrier permeability, (C) autodigestion of the wall structures by the pancreatic digestive enzymes with loss of intestinal villi and loss of mucosal barrier function. During autodigestion (panel C), the digestive enzymes enter into venules and lymphatics draining the intestine (as long as they are not themselves enzymatically digested), and they pass across the serosa into the peritoneal space. In the intestinal wall the digestive enzymes generate a variety of tissue fragments (e.g. peptide and lipid fragments) that are transported in venules and lymphatics into the portal venous and the central circulation where they act as inflammatory mediators.

tures are destroyed. Molecular absorption by the mucosal barrier and intestinal peristalsis may be severely compromised since none of the cell and membrane structures responsible for these functions remain intact. In addition, attempts to interfere with this mucosal barrier breakdown by intervening with cell signaling pathways are likely to fail, since the cells required to signal may no longer be viable or even present.

Inflammatory Mediators Generated by Digestive Enzymes in the Wall of the Intestine

Besides destruction of tissue structure, entry of digestive enzymes into the wall of the intestine generates a second problem that arises during intestinal autodigestion; that of lipolytic and proteolytic degradation of intestinal tissue with subsequent generation of proinflammatory cytotoxic mediators.

Lipases in the lumen of the intestine as part of normal digestion break dietary triglycerides into non-esterified ("free") fatty acids and glycerol. At the concentrations at which they are present these free fatty acids are cytotoxic (Penn *et al.*, 2007). When the mucosal barrier fails, these fatty acids are able to enter the intestinal wall. Moreover, the lipases that enter the intestinal wall can generate even more free fatty acids from the intestinal tissue. The body's normal defense against necrosis from free fatty acids is to bind them to proteins such as the Fatty Acid Binding Proteins and albumin, which is ubiquitous in the plasma, lymph, and interstitial spaces. However, these binding proteins in the intestine can be destroyed by pancreatic proteases that cross the mucosal barrier, preventing them from binding the free fatty acids and further liberating any free fatty acids already bound (Penn and Schmid-Schönbein, 2008). Thus, digestive enzymes may result in intestinal tissue necrosis via creation and release of free fatty acids.

Fatty acids generated in the intestine may enter the circulation, stimulating apoptosis (Dersch et al., 2005) and inflammation elsewhere. Furthermore, the intestinal necrosis itself may release many inflammatory mediators into the circulation (HMGB1, mitochondrial DNA, etc.).

Proinflammatory Signals in the System Circulation

The mixture of degrading enzymes and small molecular weight fragments generates many proinflammatory signals that are detected in the portal venous blood and in intestinal lymphatics in shock. In the early phase of shock, the liver helps absorb these inflammatory products and systemic levels the mediators remain low in spite of an ischemic intestine. However, by the time proinflammatory signals appear in the systemic circulation (e.g. in the early period of blood volume restoration in hemorrhagic shock) the first signs of multi-organ dysfunction and failure become visible (Mitsuoka *et al.*, 2000). At this point there is enhanced pulmonary permeability and interstitial lung fluid accumulation, morphological damage with microhemorrhage in the pulmonary and cardiac circulations and typical signs of in-

flammation in peripheral organs, e.g. enhanced leukocyte adhesion to the endothelium with membrane adhesion molecule expression, cytokine production, mast cell degranulation, coagulation, and eventual apoptosis (Fitzal *et al.*, 2002), to name a few of the proinflammatory events.

Evidence derived from in-vivo experimental observations is in line with the clinical evidence for proinflammatory activity in the plasma of shock victims. However, patient plasma mediators and those found in tissue may not be the same, an issue that limits the utility of biomarkers in clinical samples.

Blockade of Digestive Enzymes in the Lumen of the Intestine

It is evident from the discussion above that to prevent entry of digestive enzymes into the wall of the intestine any intervention against autodigestion requires an action against the digestive enzyme activity in the intestinal lumen; in some medical situations it may also require action against the enzyme activity in the pancreas per se. What are the possibilities in this respect?

The *first line of defense* against autodigestion is to prevent elevation of mucosal permeability in the first place or to restore its functionality as soon as possible. If the mucosal barrier has already been compromised, a second line of defense is to block the activity of digestive enzymes and minimize their ability to autodigest host tissue. The first line of defense is less of an option in many trauma situations, but may be so in elective surgery.

Instead we will focus in the following on the *second line of defense*. This approach is to block the digestive enzymes directly in the lumen of the intestine where they are in high concentrations and can be reached by direct (enteral) administration of inhibitors to these enzymes into the lumen of the intestine. In a splanchnic artery occlusion model of shock enteral blockade of digestive protease leads to a significantly reduced autodigestion of the intestinal wall, it reduces the morphological damage and the inflammatory response (Mitsuoka *et al.*, 2000; Mitsuoka *et al.*, 2002) and attenuates multiorgan failure (Fitzal *et al.*, 2002) even when administered with some delay (Fitzal *et al.*, 2004) but before major tissue damage has occurred. There is significantly less swelling of the tissues, including the lung, and reduced signs for inflammation and organ failure in peripheral tissues (Fitzal *et al.*, 2002). This protection against autodigestion and its consequences can be achieved with different protease inhibitors but is not significantly improved by the addition of an oxygen free radical inhibitor to the protease blocker or by phospholipase inhibitors (Mitsuoka and Schmid-Schönbein, 2000).

A similar protection by enteral blockade of digestive proteases against autodigestion is observed also in *endotoxic shock* (Fitzal *et al.*, 2003). If the digestive enzymes in the lumen of intestine are blocked before endotoxin administration there is transient inflammation by the endotoxin but no progression into multi-organ failure. Even though a bolus administration of endotoxin into the circulation has the ability to stimulate an inflammation response, it is tran-

sient and not *directly* responsible for the lethal course into multiorgan failure. Instead, endotoxin may elevate the mucosal permeability in the intestine, so that digestive enzymes can enter the wall of the intestine and start an autodigestion process with eventual multi-organ failure.

Enteral blockade of digestive also reduces also the need for resuscitation fluid (Doucet *et al*., 2004) and it improves morbidity after shock (Kim *et al.*, 2010). Its utility in shock or septic patients remains to be tested.

SYNOPSIS

Multiple and independent pieces of preclinical evidence support the hypothesis that the pancreatic digestive enzymes in the lumen of the intestine, an integral part of normal food digestion, can be major mediators for cell and organ dysfunction in shock. If not compartmentalized in the lumen of intestine, pancreatic serine proteases will autodigest intestinal wall structures and promote inflammation and cell and organ dysfunction (Fig. 1). There exists a possibility to block these enzymes pharmacologically in the lumen of the intestine, which in preclinical studies has led to a significant reduction of markers for multi-organ failure.

ACKNOWLEDGEMENT

Supported by GM 85072 and an unrestricted gift from Leading Ventures, San Diego, CA.

CONFLICT

Dr. Schmid-Schönbein is scientific advisor to Leading Ventures, San Diego, CA. He owns shares in Inflamagen, a company by Leading Ventures.

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BLOOD VISCOSITY MODELLING: INFLUENCE OF AGGREGATE NETWORK DYNAMICS UNDER TRANSIENT CONDITIONS

Kaliviotis E, Yianneskis M.[1]

This paper reports on a theoretical examination of the hypothesis that red blood cell network characteristics influence the mechanical properties of the fluid. For this purpose a newly developed energy-rate based blood viscosity model, which incorporates network dynamics, was used to predict the transient behaviour of blood viscosity (steady-state results of this model have been reported in Biorheology 46 (2009), 487-508). The main network characteristic examined in the present work was the inter-aggregate branch size and its relationship to the evolving aggregates. Branch size was used to define a network integrity index that accounted for the strength of the developed network. For the development and validation of the model, experiments performed with an optical shearing microscope, with different step-changes in shear rate, were utilised, as well as viscosity measurements under similar flow conditions performed in a double wall Couette instrument. The experimental data were compared with the response of the model, which incorporated the network integrity index. The results suggest that network characteristics may influence the viscosity of blood at low shear rates and exhibit good agreement with experimental observations **[Biorheology. 2011 Jan; 48(2):127-147]**.

PMID:21811017

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BIOMECHANICS OF LEUKOCYTE ROLLING

Sundd P, Pospieszalska MK, Cheung LS, Konstantopoulos K, Ley K.[1]

Leukocyte rolling on endothelial cells and other P-selectin substrates is mediated by P-selectin binding to P-selectin glycoprotein ligand-1 expressed on the tips of leukocyte microvilli. Leukocyte rolling is a result of rapid, yet balanced formation and dissociation of selectin-ligand bonds in the presence of hydrodynamic shear forces. The hydrodynamic forces acting on the bonds may either increase (catch bonds) or decrease (slip bonds) their lifetimes. The force-dependent 'catch-slip' bond kinetics are explained using the 'two pathway model' for bond dissociation. Both the 'sliding-rebinding' and the 'allosteric' mechanisms attribute 'catch-slip' bond behavior to the force-induced conformational changes in the lectin-EGF domain hinge of selectins. Below a threshold shear stress, selectins cannot mediate rolling. This 'shear-threshold' phenomenon is a consequence of shear-enhanced tethering and catch bond-enhanced rolling. Quantitative dynamic footprinting microscopy has revealed that leukocytes rolling at venular shear stresses (>0.6 Pa) undergo cellular deformation (large footprint) and form long tethers. The hydrodynamic shear force and torque acting on the rolling cell are thought to be synergistically balanced by the forces acting on tethers and stressed microvilli, however, their relative contribution remains to be determined. Thus, improvement beyond the current understanding requires in silico models that can predict both cellular and microvillus deformation and experiments that allow measurement of forces acting on individual microvilli and tethers **[Biorheology. 2011; 48(1):1-35].**

PMID:21515934

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ADENDA À LISTA DOS MEMBROS DOS ORGÃOS SOCIAIS DA SPHM (BIÉNIO 2009-2011)

NOTA CURRICULAR

Paulo Manuel de Campos Paiva Ferreira da Silva, nascido a 4 de Maio de 1965 no Porto, licenciado em Medicina pelo Instituto de Ciências Biomédicas Abel Salazar do Porto em 1989 com a classificação final de 14,3 valores. Frequentou o Internato Geral nos anos de 1990 e 1991 no Hospital Geral de Santo António, com aproveitamento. Iniciou a especialidade de Cardiologia no Centro Hospitalar de Vila Nova de Gaia em Janeiro de 1992, tendo interrompido durante um ano para cumprir o Serviço Militar Obrigatório. Obteve o grau de especialista de Cardiologia pela Sociedade Portuguesa de Cardiologia em 9 de Fevereiro de 1998 com a nota final de 19,3 valores. Desde então e até Julho do ano 2000, foi responsável pela Unidade de Cuidados Intensivos de Cardiologia do Hospital de Gaia e pela consulta de HTA e factores de risco vascular em funcionamento no Serviço de Cardiologia. Em 13 de Julho de 2000 iniciou funções no Serviço de Cardiologia do Hospital de Santo António do Porto em vaga carenciada após concurso. Concorreu para vaga do quadro de Cardiologia do Hospital de São João de Deus de Vila Nova de Famalicão, tendo sido colocado em Julho de 2001 e mantendo funções. Desde 2007 é responsável pela Unidade Funcional de Cardiologia de Famalicão, do Centro Hospitalar do Médio Ave, tendo o grau de Assistente Hospitalar Graduado. Apresentou variados trabalhos em Congressos Nacionais e Internacionais, assim como trabalhos publicados e colaborou em vários projectos de investigação e ensaios clínicos internacionais.Paralelamente com a actividade diária, colabora na formação de Médicos Internos de especialidade e técnicos de Cardiopneumologia.

REUNIÕES CIENTÍFICAS INTERNACIONAIS

2011 – 8.º CONGRESSO ASIÁTICO EM MICROCIRCULAÇÃO

The 8th Asian Congress for Microcirculation (ACM-2011) will be held in Bangkok, 26-28 October 2011.

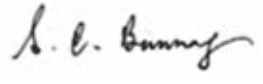
On behalf of the organizing committee, I would like to invite you to join in this special event.

The theme of this congress is **"Microvascular Biology and Bioengineering towards Regenerative Medicine".**

Under this theme, physicians, scientists and bioengineers interested in vascular diseases, stem cell and tissue engineering, and other related fields should join the event to improve our understanding of microvascular mechanisms, explored from bench to bedside leading to the biomedical engineering applications for development of techniques and therapeutic innovations.

This congress will provide a number of oral sessions, symposia, and free communication for young investigators to have scientific and friendly exchange with more experienced researchers in the field of microcirculation.

We look forward to seeing you in Bangkok at this congress, which should be a very special and memorable event for every participant.



Prof. S.C. Bunnag
(President of the Organizing Committee)
http://www.acm2011.com/

2012 – 14TH CONGRESSO INTERNACIONAL DE BIORREOLOGIA E 7.A CONFERÊNCIA INTERNACIONAL EM HEMORREOLOGIA CLÍNICA

14th International Congress of Biorheology
and 7th International Conference on Clinical Hemorheology

The Joint Meeting of International Society of Biorheology and International Society for Clinical Hemorheology

4-7 July 2012
Koç University, Istanbul, Turkey

Preliminary Topics of Scientific Sessions and Symposia

Biorheology and Biotechnology
Biorheology and Cancer
Cell-Cell and Cell-Matrix Interactions
Cellular Rheology and Biophysics
Clinical Hemorheology
Comparative Hemorheology
Endothelial Function and Shear Stress
Hemorheological Response to Therapy
Hemorheology in Hemoglobinopathies
Hemorheology and Vascular Diseases
Red Blood Cell Aggregation
Red Blood Cell Deformability
Rheological Behavior of Bio-materials
Rheology of Bio-polymers
Mechanobiology of Soft Tissues and Bone
Methodology for Rheological Testing
Molecular Rheology
Multiscale Modeling in Biorheology
Role of Nitric Oxide in Biorheology
Thrombus Formation and Mechanics

Communication

Web site: http://www.isb-isch2012.org

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The International Society of Biorheology

Newsletter Summer 2011

Letter from the President

Dear ISB Members:

I am writing to invite your participation in the triennial revitalization of our Society that usually precedes the next meeting. Following the successful joint meeting of our society with the International Society for Clinical Hemorheology, co-chaired by myself (Herb of the East) and Dr. Herbert J. Meiselman (Herb of the West) there has been a hiatus in activity as plans have developed for the next meeting. Our meeting at Penn State served to demonstrate that Biorheology remains an important field of scientific exploration with many challenges that lie ahead, and that two Herbs are better than one.

Our next meeting will be held jointly with the International Society for Clinical Hemorheology, in Istanbul, on:

July 4-7, 2012

See below for details of the meeting. To make this meeting a success, we will be soliciting proposals for symposia, as indicated in the forms below. Your proposals for symposia will be most welcome by the organizers.

In this newsletter, please find attached a dues notice. We are in need of funds to support travel awards to the Joint meeting and plenary speakers. Also included, are nomination forms for the Poiseuille Award, and Young Investigator Travel Awards. The Poiseuille Award nomination should be sent in electronic form as pdf files to the chair of the Awards Committee, Dr. Edgar O'Rear, by January 15th, 2012. Applications for young investigator travel awards will be solicited with the call for abstracts. We also encourage you to recruit new members of the Society. A blank application for membership has been included with this mailing.

I look forward to working with all of you in preparation for our next meeting and seeing you in Istanbul in July, 2012.

Best Regards,

Herbert H Lipowsky (a.k.a. Herb of the East)
President, ISB

14th International Congress of Biorheology
and
7th International Conference on Clinical Hemorheology
Istanbul, Turkey

July 4-7, 2012

Call for Symposia

SYMPOSIUM TITLE			
Chair(s) Name Mailing Address Phone/FAX/Email:			
Proposed Speakers	**Institution**	**Contacted Yes/No**	**Agreed Yes/No**
Sponsoring Society (if applicable)			
Brief Description and Rationale:			

INSTRUCTIONS:

- Please fill in this form and email to Peter Butler, pbutler@psu.edu or Gerard Nash, g.nash@bham.ac.uk: **Requested Due Date is September 30, 2011**
- Each symposium should include 4 invited speakers maximum.
- Time available for each symposium is 90 minutes.
- Symposium format: Equal division of time between speakers (e.g., for 4 speakers, 22 minutes maximum each, including Q&A).
- If you have already contacted potential speakers, please indicate 'yes' or 'no' as appropriate in the boxes under 'contacted' and 'agreed'.
- We regret that it is not possible to wave registration fees or travel funds for symposia organizers or participants.
- Criteria used to evaluate proposals will include scientific quality and relevance to conference themes, balance between clinical and basic science topics and representation of national societies.

2012 – 80.º CONGRESSO DA SOCIEDADE EUROPEIA DE ATEROSCLEROSE

http://www.eas-society.org/eas-2012-milan.aspx

REGRAS DE PUBLICAÇÃO / INSTRUCTIONS TO AUTHORS

CONVITE

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.

INSTRUÇÕES

1. Todos os textos enviados para publicação estão sujeitos a apreciação editorial e aprovação. A decisão é baseada no mérito científico e cultural dos trabalhos.

2. São aceites somente os trabalhos preparados em versão óptica (*PDF* ou *Microsoft Word*).

3. Os textos devem ser redigidos em Português ou Inglês.

4. Os manuscritos com o pedido de publicação devem ser enviados por *e-mail* ao Editor (carlotasaldanha@fm.ul.pt).

– Comunicações Originais (artigos curtos) – Os textos serão considerado para publicação rápida, com a seguinte estrutura: Sumário (50-70 palavras), Introdução, Material e Métodos, Resultados, Discussão e Conclusões. O(s) autor(es) são estimulados a englobar em conjunto os resultados, discussão e conclusões.
(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).

– Artigos de Revisão – O BOLETIM terá a maior satisfação em acolher curtas revisões sobre assuntos de particular interesse, no âmbito da Hemorreologia, Microcirculação ou assuntos de âmbito médico ou de outras áreas científicas afins, que sejam submetidos directamente para publicação ou mediante convite especial do Editor.
(Extensão máxima do texto:8 a 10 páginas (letra de corpo 11) incluindo figuras, tabelas, quadros, fotos (e respectivas legendas), agradecimentos e até 60 referências bibliográficas).

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.

INSTRUCTIONS

1. All submitted manuscripts are subjected to editorial review and approval. The decision to publish is dependent on the scientific and cultural merit of the papers.

2. Only contributions prepared and submitted as optic version (*PDF* or *Microsoft Word*), will be accepted.

3. Texts must be written in Portuguese or in English.

4. All scientific contributions, including manuscript submission and further correspondence should be addressed by *email* to the Editor (carlotasaldanha@fm.ul.pt)

– Original Communications – Manuscripts may be considered for rapid processing as short communications. All manuscripts should be arranged in the following sections: Abstract (50-70 words), Introduction, Material and Methods, Results, Discussion, Acknowledgements and References. The author(s) may combine some of the sections normally included in a full paper, namely the results, discussion and conclusions.
(Maximum communication length – 5-6 single spaced typed pages, including figures, tables, legends, acknowledgments and up to 30 references).

– Short Reviews – The BOLETIM will publish reviews on subjects of particular interest in its field, either following a special invitation or a submission by the author, and in the latter case only after approval by an Editorial Board member. Further information can be obtained from the editor.
(Maximum review length – 8-10 full pages, including figures, tables, photos, legends, acknowledgments and up to 60 references)