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Mini Review

Pattern of Circulating Micro Particles in Patients with Inflammatory Bowel Disease: Review

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Abstract

Inflammatory bowel diseases (IBD) are common group of digestive inflammatory disorder, which characterized defective regulation of adaptive immunity. There are evidences regarding intercellular cooperation affected epithelial cells, macrophages and dendritic cells plays a pivotal role in gut homeostasis. Therefore, dysregulation of this cell cooperation may lead to decreased epithelial integrity and worsening of IBD. In this report we accumulate data about causality role of circulating microparticles (MPs) in IBD and perspective of serial measurements of these biomarkers aimed risk stratification among patients with IBD. We concluded that the pattern of circulating MPs associates with disease activity, stage and histological findings of IBD and therefore it reflects risk of disease progression.

Keywords: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Risk; Circulating microparticles

Introduction

Inflammatory bowel diseases (IBD) are recognized a group of digestive inflammatory disorders characterized a wide spectrum of clinical manifestations related to typical involvement of the bowel wall [1]. As known, the idiopathic IBD comprises two types of chronic intestinal disorders: ulcerative colitis and Crohn's disease, which generally differs any regions of the involved intestine, but they have similar pathogenesis and serious variability of clinical findings [2]. Innate parameters of adaptive immunity are considered a leading trigger for both conditions: ulcerative colitis and Crohn's disease, while this phenomenon is not able to explain prevalence, epidemiology and variability of clinical settings of IBD [3]. Therefore, it has suggested that genetic polymorphism regarding nucleotide oligomerization domain 2 (NOD2), tumor necrosis factor (TNF)-SF15, interleukin-23–type 17 helper T-cell (Th17) genes and appropriate autophagy genes strongly contributes in T-helper-1- and T-helper-2-dependend impairment of immune signaling processes in Crohn's disease and ulcerative colitis [4-6]. Intraluminal bacteria and intestinal microbiota are considered the important causes mediating molecular mechanisms affected interplay of various pathogenetic factors i.e. antigenicity presentation, interactions between nitric oxide and free oxygen radicals, tissue damage with granulomatous inflammation [7-9]. Interestingly, that pathogenesis of IBD does not limit local proinflammatory responses, infections or bowel ischemia [10-12]. Defective regulation of adaptive immunity may initiate disorders in cell-to-cell cooperation, transferring information, tissue repair, angiogenesis and neovascualrization [13-16]. Indeed, crosstalk between epithelial cells, macrophages and dendritic cells plays a pivotal role in gut homeostasis [17, 18]. Moreover, dysregulation of this cell cooperation may lead to decreased epithelial integrity and worsening of chronic intestinal inflammation through IL-23-derived-, NOD2 and toll-like receptor signaling pathways [7, 19, 20]. All these findings maintain a hypothesis regarding existing of negatively effect on persistence of tissue damage and disease progression, appearance of other complications, such as cardiovascular diseases, peripheral mesenteric micro thrombosis, thromboembolism, endothelial dysfunction and vascular remodeling [21-23]. In this context, microparticles (MPs) originated from various cell types and contained biological information, peptides, active molecules, etc., may mediate multiple interactions between acquired and genetic risk factors, which are suitable for IBD. The aim of the review is summary knowledge regarding possible pathogenetic role of MPs in manifestation and progression of IBD.

Definition and Biological Role of the Microparticles

Although the biology of MPs is still incompletely unclear, the role of MPs in transfer of biological materials and cell-to-cell cooperation has determined. Overall, there are secreted membrane-enclosed vesicles, which are collectively called extracellular vesicles (EVs) and they include various types of particles, such as exosomes, ectosomes, microvesicles, microparticles, apoptotic bodies and other EV subsets predominantly distinguished sizes, immune phenotypes and origin [24]. Extracellular MPs are defined as microvesicles with sizes ranging between 50 and 1000 nm released from plasma membrane of cells different origin due to apoptosis or cell activation by specific (cytokine stimulation, mononuclear cooperation, coagulation, etc) and non-specific (shear stress) stimuli [25].

Platelet-derived MPs is the largest MPs fraction in the blood [26]. They express CD62P antigen, also known as P-select in, upon activation and continue to express it on activated platelets mediated adhesion of platelets to leukocytes especially with neutrophils [27]. Therefore, alpha-CD41 was used to assess platelet material associated with leukocytes [26]. In fact, platelet-derived MPs binding to neutrophils induced a significant increase in both CD11b expression and phagocytic activity in a concentration-dependent manner. Interestingly, P-select in co-factor named P-select in glycoprotein ligand-1 (PSGL-1) plays a crucial role in leukocyte

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activation mediating platelet-monocyte aggregation through a presence of chemokine known as RANTES [28]. Moreover, injury of endothelium leads to the swift recruitment of MPs contained tissue factor of coagulation through P-select in/PSGL-1 interactions that is trigger coagulation at site of damage [29, 30]. Finally, platelet-derived MPs are considered an activator of neutrophils and mediator, which supports ischemic injury, thrombosis and inflammation [28-30].

Leukocytic-derived MPs express CD45+ and CD54+antigens and realize due to cell activation or apoptosis. The most powerful activator for secretion of MPs from leukocytes is lipopolysacharide of Gr(-) bacteria and components of oxidative stress [31]. After secretion leukocytic-derived MPs may transfer pro-inflammatory cytokines, such as TNF, IL-6 and IL-8. They exhibit high procoagulant activity through activating inflammatory cells and transfer thromboplastin, which contains in lipid layer of MPs [32]. However, except deteriorating capacity leukocytic-derived MPs may have protective effect on endothelial cells [33]. In fact, these types of MPs including T-helper-derived MPs induce NO release, decrease production of reactive oxygen species and induce angiogenesis through activation of endothelial cells [34]. Taken together, leukocytic-derived MPs have demonstrated dual effects on the intercellular communication network and display a various potentials regarding pro-inflammatory activity, procoagulant properties in association with protective function of the endothelium [31].

Endothelial cell-derived EMPs express CD62e+, CD144+ and CD31+/CD41- antigens on their surface that allows defining it in circulation. Apoptotic-derived (CD144+ and CD31+/CD41-) or activated endothelial cell-derived (CD62e+) EMPs are capable transferring biological information, regulating peptides, hormones, proteins, lipid components without direct cell-to-cell contact to maintain cell homeostasis [35, 36]. Interestingly, circulating EMPs derived from activated endothelial cells do not contain nuclear components and they have also been shown to have pro-angiogenic and cardio-protective properties [37, 38]. In opposite, apoptotic-derived EMPs consist immune mediators, which are able to generating powerful signaling by the simultaneous receptor interaction and they are discussed a marker of endothelial cell injury and vascular aging [39, 40].

Thus, circulating MPs originated from leukocytes, platelets, and endothelial cells may have various spectrum of biological effects affected coagulation, inflammation, vascular repair and tissue protection.

Pattern of Microparticles in Inflammatory Bowel Disease

Although there are evidences that MPs different origin may involve in pathogenesis of IBD [41-44], data about their effect on disease progression and risk complications are controversial [45]. Majority investigators suggest that MPs may contribute in uncontrolled vascular-dependent intestinal damage [46, 47]. Therefore, MPs are considered a key modulator of extra intestinal complications especially in active Crohn's Disease and ulcerous colitis [47]. Indeed, Leonetti et al [48] reported that healthy volunteers and inactive Crohn's Disease patients did not differ in circulating MPs originated from platelets and endothelial cells apart from leukocyte-derived MPs. Therefore, investigators found a significant correlation between total levels of MPs, those from platelets and endothelial cells and the Harvey-Bradshaw clinical activity index. Contrary, elevated platelet-derived MPs in active patients with Crohn's Disease and ulcerative colitis were found Andoh et al [47], although healthy controls and inactive IBD patients had not differences in circulating level of platelet-derived MPs. Moreover, authors reported that significantly reduced platelet-derived MP level after achieving remission of IBD was determined. Despite data about molecular effects of circulating MPs in IBD are limited, it has suggested that type of inflammatory response underlying Crohn's disease and ulcerative colitis may determine predominantly pattern of circulating MPs. Exiting apoptotic-derived MPs may mediate tissue damage via induce an up-regulation of pro-inflammatory protein expressions, inducible NO-synthase, and cyclooxygenase-2 [45]. In contrast, secreted MPs from activated cells are considered a regulator of tissue repair and may realize protective effect on endothelium and bowel wall [38, 45, 49]. It is reasonable to assume that there is paracrine role of MPs as vectors of transcellular exchange of biological information in promoting tissue repair and vascular dysfunction in IBD [50]. Finally, to explain the causality role of circulating MPs in IBD and their potent in risk classification as a marker of progression of diseases more investigations are required.

Conclusion

It has suggested the pattern of circulating MPs associates with disease activity, stage and histological findings of IBD and therefore it reflects probability of remission and risk of disease progression. Whether serial measurements of circulating MPs if powerful tool for risk stratification of the patients with IBD is not clear ant it is required more investigations, because of individualized strategy regarding risk assessment appears to be very attractive.

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