

doi: 10.13241/j.cnki.pmb.2015.11.055

微粒在动脉粥样硬化形成及凝血异常中的作用 *

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摘要:微粒是血管内皮细胞、组织细胞或血细胞激活或凋亡时形成的亚微型囊泡。动脉粥样硬化时血浆及粥样斑块中富含多种细胞来源的微粒,不仅促进斑块的发生发展并且在动脉粥样硬化凝血异常中起重要作用,可增进血管内皮细胞和白细胞间的相互作用,使单核细胞粘附于内皮细胞,从而迁移到斑块内,吞噬清除内膜下沉积的脂质。巨噬细胞吞噬脂质后凋亡形成大量微粒,抑制内皮细胞合成释放一氧化氮,加重内皮细胞损伤,促进斑块扩大。微粒表面富含的磷脂酰丝氨酸和组织因子是微粒促凝活性的主要来源,病灶处及循环中存在的大量微粒促进了动脉粥样硬化时凝血异常的发生。本文将就微粒在动脉粥样硬化形成及凝血异常中的作用做一综述。

关键词:微粒;动脉粥样硬化;凝血异常

中图分类号:R543.5 **文献标识码:**A **文章编号:**1673-6273(2015)11-2198-03

Roles of Microparticles in the Development and Coagulant Function Abnormality of Atherosclerosis*

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ABSTRACT: Microparticles (MPs) are submicron vesicles shed from plasma membranes of vascular endothelial cells (ECs), tissue cells or blood cells in response to cell activation and/or apoptosis. Plasma and plaque in atherosclerosis are abundant in different origins of MPs, which not only contribute to the progression of this disease but play an important role in coagulant function abnormality. Microparticles facilitate interactions of ECs and leukocytes, making monocytes adherent to ECs and then migrating to the plaque for elimination of lipid. After phagocytosis, macrophages become apoptotic and deliver substantial MPs that inhibit synthesis and release of NO by ECs, rendering further injury to ECs and leading to the amplification of atheromatous plaque. Additionally, phosphatidylserine as well as tissue factor expressed on MPs impart them high procoagulant activity, thereby a great many MPs formed in lesion and circulation may accelerate the development and deteriorate the hemostatic dysfunction of atherosclerosis. In this study, we will make a concrete review about the roles of MPs in the development and the coagulant function abnormality of atherosclerosis.

Key words: Microparticles; Atherosclerosis; Coagulant dysfunction

Chinese Library Classification (CLC): R543.5 **Document code:** A

Article ID: 1673-6273(2015)11-2198-03

前言

微粒是细胞激活或凋亡时细胞膜通过出芽形式脱落的直径小于1微米的小囊泡^[1]。微粒膜外侧携带特异性母细胞源性膜抗体,并且高度表达含阴离子的磷脂酰丝氨酸 phosphatidylserine, PS^[2]。血液中的微粒来源于多种细胞,如红细胞、粒细胞、单核细胞、淋巴细胞、血小板以及血管内皮细胞。近年来研究发现多种疾病伴随微粒水平升高,尤其是存在凝血功能紊乱和血栓风险的疾病,如脓毒症、肾病综合征、系统性红斑狼疮以及多种恶性肿瘤等^[3-7]。

动脉粥样硬化 atherosclerosis, AS 是动脉硬化的血管病中最常见、最重要的一种,可累及主动脉、冠状动脉、颅脑动脉、肾动脉、肠系膜动脉以及四肢动脉等大、中动脉,主要表现为内膜下脂质沉积;单核及淋巴细胞浸润;中膜平滑肌细胞迁移至内膜并大量增殖;单核细胞和平滑肌细胞摄取脂质变成泡沫细胞,进而形成动脉粥样斑块^[8]。动脉粥样斑块突出于动脉管腔造成血管狭窄,导致血液供应障碍,产生缺血或坏死;若斑块破裂诱发血栓形成,则会危及生命。动脉粥样硬化时血浆和粥样斑块中存在大量微粒,这些微粒参与动脉粥样硬化的发生发展并且具有高促凝活性,在动脉粥样硬化凝血紊乱中也起到重要的

* 基金项目:国家自然科学基金项目(81270588)

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(收稿日期:2014-07-25 接受日期:2014-08-18)

作用。

1 动脉粥样硬化中微粒的来源

1.1 斑块微粒

动脉粥样硬化是一种慢性炎症性疾病,以血管内皮细胞损伤和炎症细胞浸润为特征^[9]。在长期高脂血症的情况下,增高的脂蛋白中主要是氧化修饰的低密度脂蛋白(oxLDL)和胆固醇对动脉内膜造成功能性损伤,使内皮细胞表面粘附分子表达增加,同时释放细胞因子和趋化因子,促使白细胞(单核细胞和淋巴细胞)粘附到内皮细胞表面,并从内皮细胞之间游移到内膜下成为巨噬细胞,通过清道夫受体吞噬 oxLDL,转变成泡沫细胞形成最早的粥样硬化病变脂质条纹。巨噬细胞吞噬脂质的同时发生凋亡,形成大量微粒,而损伤的内皮细胞也会产生微粒释放到血液中或参与粥样斑块的形成。

平滑肌细胞增生在动脉粥样斑块发生及发展中也起到重要作用。内皮细胞损伤释放内皮细胞生长因子,促进血管内膜及平滑肌细胞增殖^[10]。同时,血管内皮损伤暴露内膜下组织,激活血小板释放多种细胞因子,如血小板源性生长因子,促进中膜平滑肌细胞迁移增殖^[11]。平滑肌细胞释放大量的胶原纤维等结缔组织基质参与粥样斑块纤维帽的形成。此外,平滑肌细胞也能够吞噬脂质颗粒形成泡沫细胞,从而释放大量微粒。

Leroyer 等^[12]对动脉粥样斑块中微粒来源的分析显示,白细胞微粒的比例最大(约 52%),其中巨噬细胞占 29%,淋巴细胞占 15%,中性粒细胞占 8%。红细胞微粒和内皮细胞微粒分别占微粒总数的 27%和 8%。血小板微粒较少见。粥样斑块较血浆特异的平滑肌细胞微粒约占总微粒的 13%。

1.2 循环微粒

在血流动力学发生变化的情况下,如血管局部狭窄产生的湍流和血流剪切力变化时,使局部血细胞激活形成微粒。血小板对血液流变较为敏感,并且在凝血酶、ADP 等促凝物质作用下迅速激活形成血小板微粒,是血液中微粒的主要来源。单核细胞和内皮细胞在脂蛋白、氧化应激及炎症细胞因子如肿瘤坏死因子和白细胞介素等的作用下激活,形成微粒释放到循环中^[13]。

2 微粒在动脉粥样斑块发生发展中的作用

2.1 促进内皮细胞与白细胞的相互作用

Pierre-Emmanuel Rautou 等^[14]发现采用颈动脉内膜切除术病人斑块中的微粒处理内皮细胞,内皮细胞间粘附分子(inter-cellular adhesion molecule, ICAM-1) 的表达水平随时间和浓度的增加而上调。ICAM-1 作为重要的内皮细胞粘附分子,其主要功能是与淋巴细胞相关功能抗原 1(lymphocyte function associated antigen-1, LFA-1)的结合,介导白细胞的粘附与迁移。因此,粥样斑块中的微粒可能促进白细胞与内皮细胞间的相互作用,促进炎症的发展,进而促进粥样斑块的形成^[24-26]。

2.2 抑制内皮细胞的正常功能

研究表明,微粒还能影响内皮细胞的正常生理功能,如微粒抑制内皮细胞合成及释放 NO,增加其过氧化物的产生,使内

皮细胞功能障碍导致血管舒张受限^[15]。Mezentsev 等^[16]观察发现随着微粒浓度和作用时间的增加,内皮细胞增殖率下降而凋亡率增加,表明微粒抑制内皮细胞的修复功能,加重内皮细胞功能损伤。如果大量微粒不能及时有效地被清除,将直接损害内皮细胞功能或者激活炎症细胞释放炎症介质,促使动脉粥样斑块进一步恶化^[27,28]。

3 微粒在动脉粥样硬化凝血异常中的作用

细胞激活或凋亡时,细胞内钙浓度增加,致使细胞膜不对称性丧失,PS 暴露于细胞膜外表面,细胞膜以囊泡形式脱落即形成微粒^[17]。因此,微粒膜外表面富含 PS。细胞膜 PS 能够为凝血因子提供催化表面,促进内外源性 X 因子转化为因子 Xa,凝血酶原转化为凝血酶^[18,20]。越来越多的研究表明,表达 PS 的微粒在多种疾病中显著增多,并且在凝血紊乱中起到重要作用。白细胞、内皮细胞以及平滑肌细胞来源的微粒表面携带组织因子 tissue factor, TF。组织因子是启动外源性凝血的主要物质,也是微粒促凝活性的来源之一^[21]。

动脉粥样硬化患者血液中微粒总数较正常对照显著增高,并以血小板来源的微粒最为明显^[22]。血小板是参与凝血反应的主要细胞,而血小板微粒的促凝活性较血小板高 50-100 倍^[23]。因此,动脉粥样硬化患者循环中增加的血小板微粒可能诱发全身高凝状态^[29]。不稳定型动脉粥样斑块,其纤维帽较薄,脂质池较大易于破裂。动脉粥样斑块破裂释放大量脂质,微粒及细胞碎片诱发急性血栓形成,严重危及生命^[30]。Leroyer 等^[12]通过对 26 例颈动脉内膜切除术患者和健康对照组相比较发现,斑块内的微粒浓度至少比血浆中高 200 倍,且比循环中的微粒容易聚集形成血栓。上述研究结果表明动脉粥样硬化时,大量微粒的生成与其凝血功能紊乱密切相关。

4 小结

动脉粥样硬化时,血液及斑块中形成的多种细胞来源的微粒在粥样斑块发生发展及动脉硬化凝血异常中起到重要作用。随着对微粒研究的增加,其可能成为评价动脉粥样硬化早期细胞活化或凋亡以及凝血活性的新指标,但现有的微粒检测方法无法在疾病早期敏感准确地检测微粒的数目及来源。因此,微粒的检测手段有待于进一步提高,在动脉粥样硬化中通过监测微粒来源及数目分析疾病的发生发展及凝血活性将为临床诊断及治疗提供新思路。

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