The Role of Microparticles in the Pathogenesis of Rheumatic Diseases

Essay

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ABSTRACT

Microparticles (MPs) are membrane-bound vesicles that can act as unique signaling elements in the pathogenesis of rheumatic diseases. MPs originating from platelets, leukocytes, endothelial cells and erythrocytes are found in circulating blood at relative concentrations determined by pathophysiological context. Once released from cells by membrane blebbing, MPs display diverse functional activities and can mediate intercellular communication. Importantly, in the context of rheumatic diseases, MPs can regulate thrombosis, vascular reactivity, angiogenesis and inflammation. Consistent with the role of MPs in immunopathogenesis, patients with rheumatic diseases show marked increase in the number of particles in the blood, which can reflect the extent and severity of the diseases. MPs are now emerging as new biomarkers from a specific tissue undergoing activation or damage. Thus detection of MPs in the circulating blood, would not only improve our comprehension of disease pathogenesis, but also constitute a powerful tool as a biomarker in the prediction, diagnosis, prognosis and follow up of rheumatic diseases.

Key words:

Microparticles - Rheumatic diseases - Pathogenesis .

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LIST of ABBREVIATIONS

AAV	Anti-neutrophil cytoplasmic antibody associated vasculitis.
aCL	Anticardiolipin .
ADP	Adenosine diphosphate .
AECAs	Anti-endothelial cell antibodies .
AIDs	Autoimmune diseases.
ANA	Antinuclear antibodies .
ANCA	Ant i-neutrophil cytoplasmic antibodies .
aPL	Antiphospholipid antibody.
APS	Antiphospholipid syndrome .
ATP	Adenosine triphosphate .
C	Complement .
CI	Collagen type I.
Ca	Calcium .
Ca++	Calcium ions .
CCL	Chemokine ligand .
CD	Cluster of differentiation .
CK	Creatine kinase .
CR 1	Complement receptor 1.

CRP	C-reactive protein .
CTD	Connective tissue disease .
DAS	Disease activity score .
DM	Dermatomyositis.
DNA	Deoxyribonucleic acid .
ECs	Endothelial cells .
ELISA	Enzyme-linked immunosorbent assay .
EMPs	Endothelial microparticles .
ETP	Endogenous thrombin potential .
FC	Flow-cytometry .
g	Relative centrifuge force.
GP	Glycoprotein .
GPI	Glycosylphosphatiylinositol .
HMG COA	Hydroxy methylglutary coenzyme A .
ICAM-1	Intercellular adhesion molecule-1.
IFN-ɤ	Interferon-gamma .
Ig	Immunoglobulin .
IgG	Immunoglobulin G .
IL	Interleukin .
ITP	Idiopathic thrombocytopenic purpura .

LA	Lupus anticoagulant .
LCAP	Leukocytapheresis .
LDL	Low-density lipoprotein .
LMPs	Leukocyte-derived microparticles .
Mg++	Magnesium ions .
MHC	Major histocompatibility complex .
MMPs	Matrix metalloproteinases .
MPs	Microparticles .
mRNA	Messenger ribonucleic acid.
MRSS	Modified Rodnan skin thickness score .
NO	Nitric oxide .
nm	Nanometer .
PAMPs	Pathogen-associated molecular patterns.
PAPS	Primary antiphospholipid syndrome .
PC	Phosphatidylcholine .
PDGF	Platelet derived growth factor .
PE	Phosphatidylethanolamine .
PECAM-1	Platelet endothelial cell adhesion molecule-1.
PFP	Platelet-free plasma .
PGE2	Prostaglandin E2 .

PM	Polymyositis .
PMPs	Platelet-derived microparticles .
PS	Phosphatidylserine .
pSS	Primary Sjogren syndrome .
RA	Rheumatoid arthritis .
RBCs	Red blood cells .
RNA	Ribonucleic acid .
ROCK I	Rho-associated kinase I .
sCDL	Soluble cluster of differentiation ligand.
SLE	Systemic lupus erythematosus.
SM	Sphingomyelin.
SSs	Systemic sclerosis .
TAT	Thrombin anti-thrombin .
TF	Tissue factor.
TGF-β	Transforming growth factor-beta .
TH-1	T helper-1.
TIMP	Tissue inhibitor metalloproteinases .
TNF-α	Tumor necrosis factor-alpha .
tRNA	Transfer ribonucleic acid.
µm	Micrometer.
VCAM-1	Vascular cell adhesion molecule-1.
WBCs	White blood cells .

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Introduction and Aim of the Study

Introduction

Microparticles (MPs) are a heterogenous population of small, membrane-bound vesicles which are released from activated or dying cells, and can act as unique signaling elements in the pathogenesis of rheumatic diseases ***(Beyer and Pisetesky,2009).***

MPs were first described in 1967 when **Wolf** described the presence of fragments derived from platelets in human plasma. He called these fragments 'platelet dust'. This 'dust' contained vesicles, smaller than 0.1µm in diameter, these vesicles were later called MPs. Release of MPs has been reported in several circumstances in normal physiology as well as in disease states. These vesicles have been implicated to play a role in inflammation, coagulation and diseases associated with impairment of vascular function ***(Brodsky et al.,2004).***

During the last 20-30 years extensive research has been done on cell-derived MPs. We now know that they can be released not only from platelets, but also from erythrocytes, leukocytes, endothelial cells, and other cell types, and that such MPs are not only present in the circulation but also in other body fluids, such as synovial and cerebrospinal fluids***(Morel et al.,2009).*** MPs are released from any cell types during activation or apoptosis, their generation seems to be a well-regulated process ***(Hughes et al.,2000).***

The release of membrane MPs and endothelial damage are key steps in the pathogenesis of inflammation. At the site of endothelial injury, secretion of pro-inflammatory cytokines and expression of cyto-adhesions by endothelial cells are well described features involved in the recruitment of inflammatory cells. The concomitant breakdown of the endothelial barrier enables infilteration of the vascular wall or perivascular space by cells or mediators capable of perpetuating the inflammatory response. Having long been considered as inert remenants of cell destruction or markers of cell death, MPs shed by apoptotic or damaged cells are known to behave as potent regulators of endothelial function. They contribute to a long range transmission of biological information that may ultimately alter endothelial function itself ***(Morel et al.,2006).***

The pathogenesis of inflammatory rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitides, and antiphospholipid syndrome is incompletely understood, but increasing evidence suggests that MPs play an important role in the pathogenesis of these diseases by regulating thrombosis, vascular reactivity and inflammation. Also MPs have an increasingly recognized role in immunopathogenesis. Consistent with a role of MPs in immunopathogenesis, patients with rheumatic diseases show marked increase in the number of MPs in the blood, which can reflect the extent and severity of the disease ***(Ardoin et al.,2007).***

In general, biomarkers represent products of cells (for example, cytokines) or functional changes in cells which are usually sampled from the blood. These changes include the expression of cell surface markers or patterns of gene expression. MPs provide a link between inflammation, coagulation, and angiogenesis, which are the key processes in both systemic and organ-specific disease manifestations ***(Beyer and Pisetsky, 2009).*** Because they can be quantified in blood, MPs represent novel biomarkers for otherwise inaccessible tissues (such as endothelium) that are important sites of inflammation and damage. The development of biomarkers for autoimmunity is very important in determining disease pathogenesis and assessing disease activity in routine care as well as in clinical trials ***(Pisetsky,2009).***

Aim of the Study

Is to demonstrate a detailed review discussing the origin, composition as well as the activity of MPs and to describe the role of MPs as novel biomarkers for autoimmunity in an attempt to elucidate the pathogenesis of rheumatic diseases.