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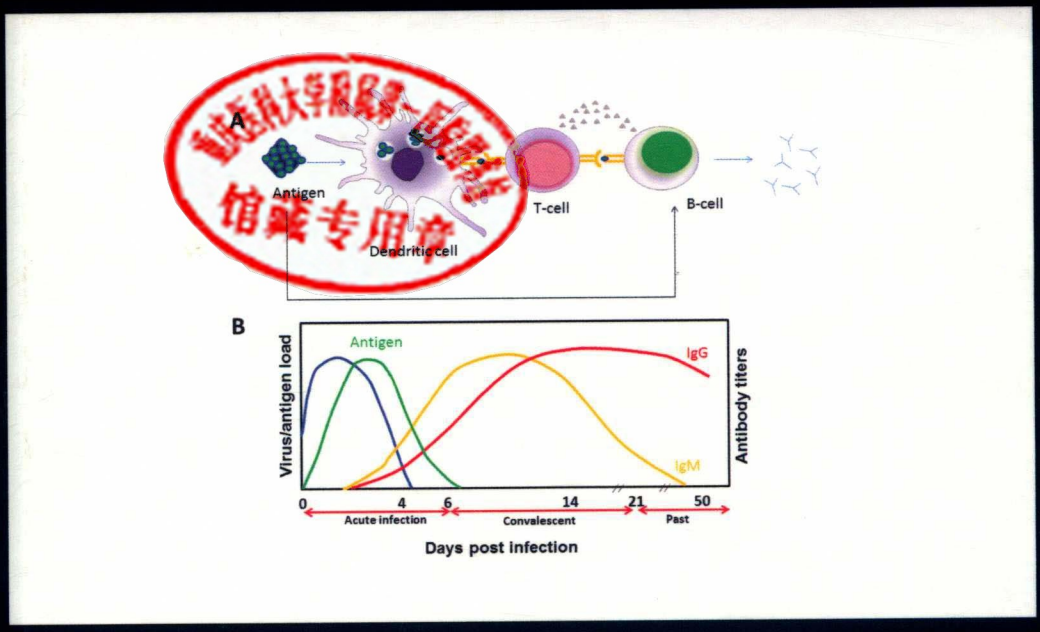

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Gregory S. Makowski

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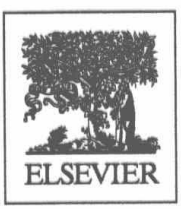

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VOLUME EIGHTY ONE

ADVANCES IN CLINICAL CHEMISTRY

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PREFACE

The fourth volume of the *Advances in Clinical Chemistry* series for 2017 is presented.

In Chapter 1, the role of circulating microparticles in the diagnosis and prognosis of heart failure is reviewed. Microparticles, a heterogeneous subpopulation of extracellular vesicles containing markers derived from their cell of origin, are continuing to stimulate considerable study and research as diagnostic and potentially therapeutic tools in many disease processes including heart failure. In Chapter 2, the importance of peptide antibodies in clinical laboratory diagnostics is explored. Due to their high specificity and sensitivity, these multifunctional molecules are indispensable in the generation of novel clinical assays for the identification and quantification of disease markers. In Chapter 3, biomarkers of bone turnover are highlighted with emphasis on the c-terminal cross-linked telopeptide for type I collagen. Accurate assessment of bone status remains a continuing clinical problem due to the potential for catastrophic nontraumatic fracture in the growing elderly population. In Chapter 4, testing for human papilloma virus, the causative agent in cervical cancer, is reviewed. The molecular basis of this virus, its pathogenesis, and the epidemiology of infection will be discussed. Guidelines for cervical cancer screening and treatment will also be considered. In Chapter 5, the role of exercise in physiology and pathophysiology will be explored. Although low-intensity physical activity is considered beneficial, strenuous exercise may enhance inflammation and trigger the generation of free radicals, thus mediating damage to intracellular targets including DNA. In Chapter 6, damage to nucleic acid via the generation of bulky chemical complexes, i.e., adducts, is reviewed with emphasis on smoking and lung cancer. The generation of large reactive electrophiles during detoxification increases adduct risk and can lead to mutations in oncogenes/tumor suppressor genes, thus promoting carcinogenesis.

I thank Volume 81 contributors and colleagues for their peer review. I extend thanks to Shellie Bryant and Vignesh Tamilselvvan for expert editorial support.

I hope the fourth volume for 2017 will be enjoyed. Comments and feedback from the readership are always appreciated.

I would like to dedicate Volume 81 to Chris on the occasion of his 40th birthday.

GREGORY S. MAKOWSKI

CONTENTS

CHAPTER ONE

Microparticles in Chronic Heart Failure

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Contents

Abstract

Heart failure (HF) continues to have a sufficient impact on morbidity, mortality, and disability in developed countries. Growing evidence supports the hypothesis that microparticles (MPs) might contribute to the pathogenesis of the HF development playing a pivotal role in the regulation of the endogenous repair system, thrombosis, coagulation, inflammation, immunity, and metabolic memory phenomenon. Therefore, there is a

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large body of data clarifying the predictive value of MP numerous in circulation among subjects with HF. Although the determination of MP signature is better than measurement of single MP circulating level, there is not yet close confirmation that immune phenotype of cells produced MPs are important for HF prediction and development. The aim of the chapter is to summarize knowledge regarding the role of various MPs in diagnosis and prognosis of HF. The role of MPs as a delivery vehicle for drugs attenuated cardiac remodeling is considered.

ABBREVIATIONS

BNP brain natriuretic peptide
CV cardiovascular
EVs extracellular vesicles
HF heart failure
HFpEF chronic HF with preserved ejection fraction
HFrEF chronic HF with reduced ejection fraction
HSP heart shock protein
ICAM intracellular adhesion molecule
MI myocardial infarction
MPs microparticles
PGF placental growth factor
PLGA poly(lactic-*co*-glycolic acid)
STEMI ST-segment elevation myocardial infarction
VCAM vascular cell adhesion molecule
VEGF vascular endothelial growth factor

1. INTRODUCTION

Heart failure (HF) continues to have a sufficient impact on morbidity, mortality, and disability in developed countries [1]. However, within last decades, the prevalence of HF have been progressively decreased predominantly HF with reduced left ventricular ejection fraction (HFrEF) [2]. In contrast, frequency of novel cases of HF with preserved left ventricular ejection fraction (HFpEF) appears to be raised [3]. These changes in epidemiology of HF depend in particularly on the implementation of contemporary strategy regarding early diagnosis, prevention, treatment of HF [4], as well as resulting in effect of aging, sex, socioeconomic status, and comorbidities [5–8].

Cardiac dysfunction that accompanies various types of HF development is a complex and rather controversial issue and results from the trophic effects

of pure mechanical overload, and susceptibility factors (i.e., ischemia, inflammation, overload, dysmetabolic reasons) and the neurohormonal reaction [9]. There are current available data regarding the role of cardiac remodeling, worsening of adrenergic signaling mechanisms in the cardiac response, catecholamines toxicity, inflammation, thrombosis, worsening of endothelial integrity, and endothelium injuries are common for HF onset and development beyond etiology [9–12]. Indeed, there are evidence regarding the important role of dysregulation of sympathetic nervous system and renin–angiotensin–aldosterone system (RAAS) in the HF [9,13]. To our knowledge, adrenal signaling and RAAS overdrive accompany non-cardiovascular (non-CV) pathologies (i.e., hyperglycemia and diabetes mellitus, obesity and metabolic syndrome, obstructive sleep apnea, and renal disease) with cardiac impairment [12,13]. Moreover, dysregulation of intracellular signaling mechanisms in HF is considered a determined higher risk of arrhythmias and cardiac remodeling contributing to worsen the prognosis of this disease [13]. In this context, the investigations regarding the underlying molecular mechanisms of failing heart could be promised in the discovery of novel diagnostic tools and predictive biomarkers in several phenotypes of HF.

Nevertheless, male gender, current smoker status, increased highly sensitive troponin T, and previous myocardial infarction (MI) were associated with new onset HFrEF, whereas female gender, history of atrial fibrillation, increased urinary albumin excretion, and cystatin C were conferred new onset HFpEF [14]. However, higher age, obesity, and increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) increased the risk for both HFpEF and HFrEF [14].

Although improving the management of HF remains a priority for health care services, the outcome of HF patients remains poor despite modern pharmacological and none-pharmacological therapies including established devices, i.e., cardiac resynchronization therapy devices and implantable defibrillator/cardioverters [8,15]. Furthermore, the clinical outcomes of both phenotypes of HF have been occurred similar or at least not sufficiently distinguished [16] that is important challenge for contemporary medical care service.

There is growing awareness of the role of several predictive tools reflecting various pathophysiological stages of cardiac dysfunction development for risk stratification of the patients with various of HF. Most studies have described the utility of biological markers in HF for diagnosis,

prediction, and even biomarker-guided therapy, but by now natriuretic peptides, soluble ST2, galectin-3, and high-sensitive cardiac specific troponins were validated only [4,17]. As expected, the routine use of biomarkers on diagnosis of HF might help to stratify the patients at higher risk of death and clinical outcomes. In fact, both 2012 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure and 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Management of Heart Failure are well accepted by many clinicians regarding diagnosis and prognosis of HFrEF. In contrast, diagnosis and prediction of HFpEF with biomarkers is still challenging for practitioners [18]. However, there was not a large body of evidence regarding perspectives to may provide clinically useful prognostic information both concerning the future risk of HFpEF/HFrEF manifestation in asymptomatic subjects, the risk of fatal events, and primary/readmissions in the hospital in individuals for those have already established symptomatic acute, acutely decompensated/advanced, and chronic stable HF related to ischemic and nonischemic causes [19]. It is suggested that multimorbidity in HF may limit the diagnostic and predictive utility of biomarkers [20–22]. HF may closely associate with release of newly detectable circulating biomarkers currently called microparticles (MPs) [23,24]. The aim of the chapter is to summarize knowledge regarding the role of various MPs in diagnosis and prognosis of HF.

2. DEFINITION, CLASSIFICATION, STRUCTURE, AND REGULATION OF MPs

MPs are defined a heterogeneous subpopulation of extracellular vesicles (EVs) with diameter average from 100 to 1000 nm originated from plasma membranes of mother' cells (Table 1). EVs are phospholipid-based endogenously produced particles (30–1000 nm in diameter), which contain cell-specific collections of proteins, glycoproteins, lipids, nucleic acids, and other molecules. Abundant cells including cardiomyocites, blood cells, endothelial cells, immune cells, and even tumor cells are capable to secrete MPs of different size and compositions [25].

Depending on their origin EVs are graduated to follow subsets, i.e., the exosomes (30–100 nm in diameter), the microvesicles (50–1000 nm in diameter), ectosomes (100–350 nm in diameter), small-size MPs (<50 nm

Table 1 Classification and Key Features of Extracellular Vesicles

Population of Vesicles	Diameter (nm)	Origin	Main Contained Components	Best-Characterized Cellular Sources	Markers
EV	30–1000 nm	Cell membranes	Regulatory proteins (i.e., heat-shock proteins, tetraspanin), lipids, active molecules, nucleic acids (mRNA, miRNA), cytokines, growth factors, hormones, procoagulant phosphatidylserine, likely complement	All cell types	Annexin V binding, tissue factor, and cell-specific markers
MPs	100–1000 nm	Plasma membranes		Platelets, RBC, and endothelial cells	
MV	50–1000 nm	Plasma membranes		Platelets, RBC, and endothelial cells	
Small-size MPs	<50 nm	Plasma membranes		Endothelial cells	CD133+, CD63−
Exosomes	30–100 nm	Endosomal membranes		Immune cells and tumors	CD63, CD61, CD63, CD81, CD9, LAMP1, and TSG101
Ectosomes	100–350 nm	Plasma membranes		Platelets, RBC, activated neutrophils, and endothelial cells	TyA, C1q
Late endosomes	50–1000 nm	Endosomal membranes	Close-packed luminal vesicles	Immune cells and tumors	Annexin V binding, DNA content
Apoptotic bodies	0.5–3.0 μm	Plasma membranes	Proapoptotic molecules, oncogenic receptors	Cell lines	

Abbreviations: *EVs*, extracellular vesicles; *MPs*, microparticles; *MV*, microvesicles; *RBC*, red blood cells.

in diameter) known as membrane particles and apoptotic bodies (1–5 μm in diameter).

The exosomes are formed by inward budding of the endosomal membrane and are released on the exocytosis of multivesicular bodies known as late endosomes, whereas the microvesicles are attributed via budding from plasma membranes. However, the exosomes have been predominantly labeled in the case of immune cells (macrophages, T cells, B cells, and dendritic cells) and tumor cells. Unlike the exosomes, the ectosomes are ubiquitous microvesicles assembled at and released from the plasma membrane [26].

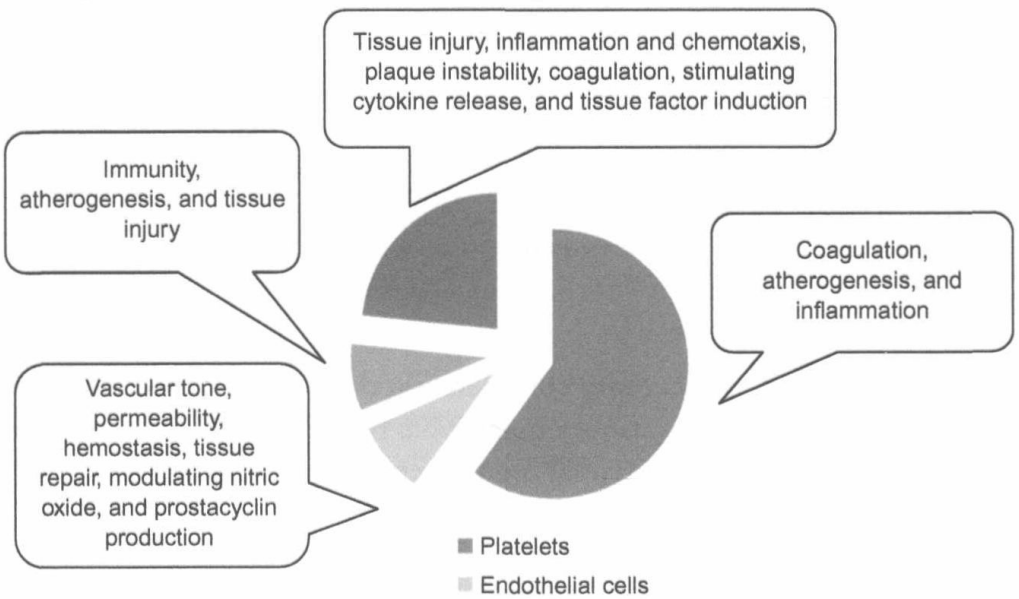
MPs are released by cellular vesiculation and fission of the membrane of cells [27]. Under normal physiological condition, a phospholipid bilayer of plasma membrane of cells represented phosphatidylserine and phosphatidylethanoalamine in inner leaflets, whereas phosphatidylcholine and sphingomyelin represent in the external leaflets. The asymmetrical distribution of phospholipids in the plasma membrane is supported by activity of three major intracellular ATP-dependent enzyme systems, i.e., flippase, floppase, and scramblase. Because aminophospholipids are negatively charged, but phospholipids exhibit neutral charge, the main role of intracellular enzyme systems is supporting electrochemical gradient. Both flippase and floppase belong to the family of ATP-dependent phospholipid translocases. The flippase translocates phosphatidylserine and phosphatidylethanoalamine from the external leaflets to the inner one. The floppase transports phospholipids in the opposite direction. Finally, scramblase being to Ca^{2+}-dependent enzyme system exhibits unspecific ability of moving of phospholipids between both leaflets of plasma membrane.

Importantly, disappearing of the asymmetrical phospholipid distribution in the bilayer of the cell membrane is considered a clue for vesiculation and forming of MPs. Indeed, both processes of apoptosis or cell activation are required asymmetry in phospholipid distribution that leads to cytoskeleton modifications, membrane budding, and MPs release. The mechanisms of vesiculation directly affect genome and may mediate by some triggers including inflammation [28], while in some cases, there is a spontaneous release of MPs from stable cells or due to injury from necrotic cells or from mechanically damaged cells. Particularly, the MPs are released in both constitutive and controlled manners, regulated by intercellular Ca^{2+} and Rab-GTP-ases and activation of μ-calpain. μ-Calpain is a Ca^{2+}-dependent

cytosolic enzyme belong to protease, which cleaves talin and α-actin, leading to decreased binding of integrins to the cytoskeleton and a reduction in cell adhesion and integrity. Finally, interaction of the actin and myosin is a main component for cytoskeleton modification that creates a contractile force and drives the formation of membrane MPs.

Recently MPs are considered a cargo for various molecules. Indeed, MPs carry proteins, RNA, micro-RNA, and DNA fragments from their cells of origin to other parts of the body via blood and other body fluids. Within last decade, it has become to know that MPs would act as information transfer for target cells. However, the difference between innate mechanisms affected the release of MPs from stable cells, activated cells, or apoptotic cells is yet not fully investigated and requires more studies.

The majority (more than 90%) of MPs in healthy controls are of platelet origin, whereas less than 10% originate from granulocytes and less than 5% from endothelial cells, red blood cells, and monocytes [29]. Since all types of particles contain surface proteins derived from their cell of origin (including antigen-presenting cells), while there are additional biomarkers confirming origin of the MPs (Fig. 1). The key features of several MP populations are



Abbreviation: *APCs*, antigen-presenting cells

Fig. 1 Origin and main biological function of several MPs.