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Review

Role of extracellular vesicles in autoimmune diseases

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ABSTRACT

Extracellular vesicles (EVs) consist of exosomes released upon fusion of multivesicular bodies with the cell plasma membrane and microparticles shed directly from the cell membrane of many cell types. EVs can mediate cell–cell communication and are involved in many processes including inflammation, immune signaling, angiogenesis, stress response, senescence, proliferation, and cell differentiation. Accumulating evidence reveals that EVs act in the establishment, maintenance and modulation of autoimmune processes among several others involved in cancer and cardiovascular complications. EVs could also present biomedical applications, as disease biomarkers and therapeutic targets or agents for drug delivery.

Contents

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1. Introduction

Extracellular vesicles (EVs) are a heterogeneous family of extracellular structures bounded by a phospholipid bilayer and released by all cell types in various biological fluids. They contain and expose at their membrane surface protein and lipid components as well as nucleic acids originating from their original cell [1,2]. EVs are considered to consist of two main families: the exosomes and the microparticles (MPs) which are distinguished by their size, their mechanism of formation and their composition [3] as shown in Fig. 1. It is commonly recognized that EVs have various biological functions involved in different processes such as inflammation, immune signaling, coagulation, vascular reactivity, angiogenesis and tissue repair [1,4]. They mediate intercellular communication and can also act as platform for enzymatic processes. These characteristics give to EVs an increasingly documented role in physiological processes. EVs are also considered as potential biomarkers of activity or cell death and have been proposed as agents for drug delivery [5]. Their involvement in various pathological mechanisms represents a new area of research, particularly in pathogenesis of autoimmune diseases [4,6].

2. Exosomes and MPs

Exosomes and MPs form the two main populations of EVs. The border between these two types of EVs is however tenuous as both structures share common characteristics. Moreover, this distribution according to their size is probably not very relevant in vivo [7]. In theory, EVs are produced by all cell types including immune cells and are found in all body fluids (blood, urine, saliva, cerebrospinal fluid, breastmilk, amniotic fluid, ascites, bile and semen).

Exosomes have a size between 50 and 100 nm and derive from endocytic compartment [1–3,8]. They are generated by invagination of the endosomal membrane resulting in the formation of intraluminal vesicles in endosomal multivesicular body [9–11]. During the invagination process, cytosolic cell components are encapsulated inside vesicles and molecules present on endosomal membrane such as MHC molecules are expressed on the vesicle membrane. Then, the endosome fuses with plasma membrane releasing into extracellular medium the intraluminal vesicles called exosomes. Their production can be spontaneous [12] or induced by various stimuli [13,14] depending on cell types. The biochemical composition of exosomes is variable depending on their cell origin; nevertheless some constituents are found in a wide proportion of exosomes and can be considered as identification markers without being totally specific. Complementary proteomics and lipidomics approaches are useful to study the composition of exosomes as well as other EVs [15,16]. Generally, exosomes are surrounded by a phospholipid bilayer enriched with cholesterol, sphingomyelin and ceramide [17,18]. The presence of phosphatidylserine (PS) at the surface of exosomes differs depending on studies. Indeed, some studies showed that exosomes do not express PS on their surface [19,20] while PS has

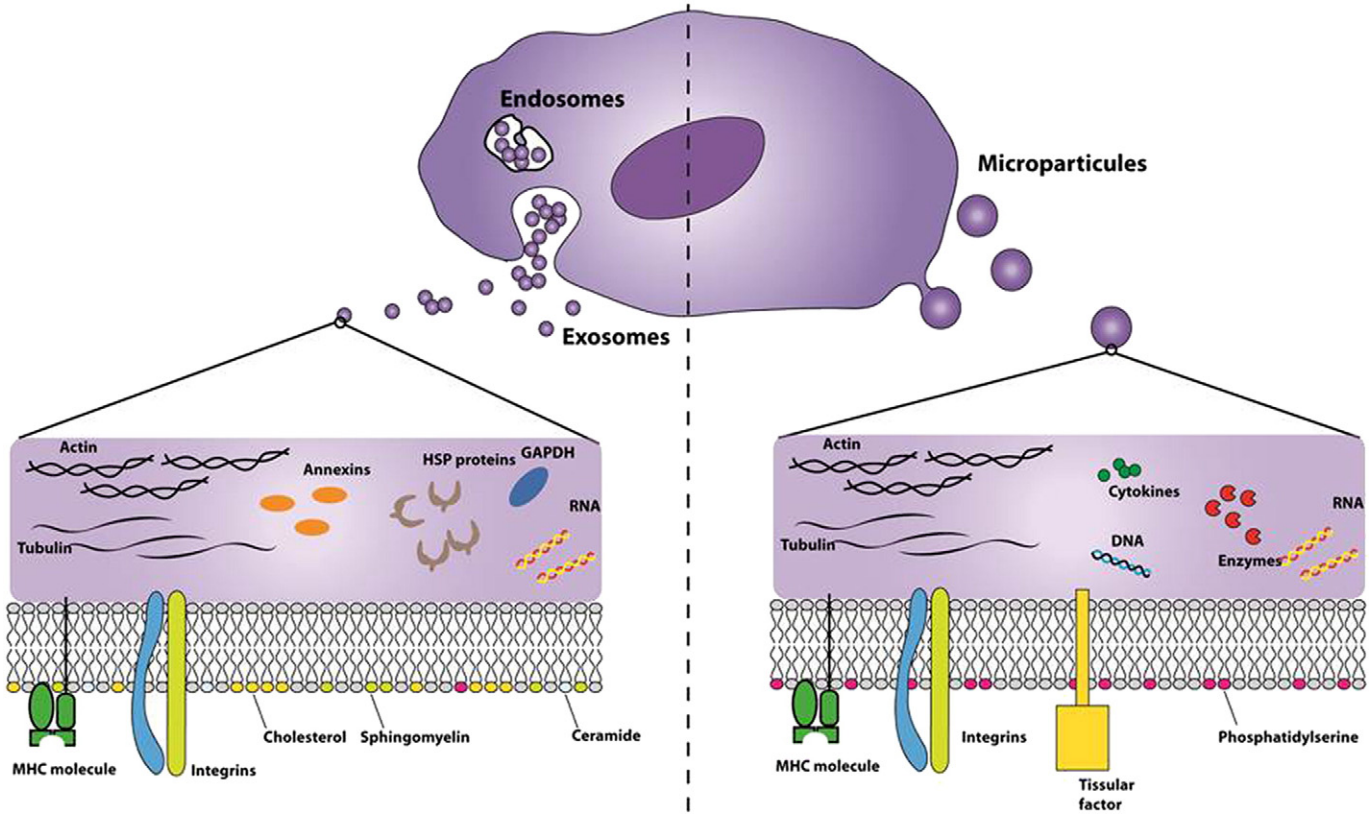

Fig. 1. Formation and composition of microparticles and exosomes.