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Review

Host derived exosomes-pathogens interactions: Potential functions of exosomes in pathogen infection

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ABSTRACT

As bilayer vesicular corpuscles secreted by different living cells, exosomes can be found in diverse body fluids and are rich in lipids, proteins, nucleic acids and other complicated components. Exosomes offer a potent mechanism for participation in intercellular transportation, such as targeted transmission of inclusions to nearby or distant cells or tissues, and assistance in intercellular information communication to change physiological functions and properties. Exosomes take part in antigen presentation for activation of immune cells and stimulate the release of inflammatory factors and the expression of immune molecules, thus modulating the immune responses of host cells. In the microbial infection of host cells, exosomes can strengthen innate and specific immune responses and thereby the immune resistance against the invading microbes through natural killer cells, macrophages and activated T cells by the presentation of pathogens including viral factors and bacteria, but exosomes are also capable of immunosuppression during pathogens infection. Exosomes are considerably valuable in research and clinical defense of microbial infection, given their biological activities in intercellular transportation, information communication and cell-mediated immunity modulation after microbial infection.

1. Introduction

In 1980s, Johnstone et al. found a type of small membranous vesicles in the supernatant of sheep red blood cells cultured *in vitro* and named them exosomes, which are lipid bilayer vesicles in density of 1.13–1.19 g/mL and even size of 30–100 nm [1]. Exosomes biogenesis proceed in four steps: origination, endocytosis, multivesicular endosomes (MVE) generation, and secretion [2]. During the biogenesis, the plasma membranes invaginate the various extracellular parts and membrane receptors in early endosomes, and then early endosomes develop into late endosomes [3,4]. When the inner membranes of late endosomes bud, small intraluminal vesicles (ILVs) gather into MVEs [5] and consequently, proteins, lipids and cytosolic parts are all sequestrated. Though MVEs fuse with lysosomes to degrade cargoes, some exosomes fuse with plasma membranes to discharge ILVs as exosomes [6]. Actually, eukaryotic cells release another type of vesicles- ectosomes formed at plasma membranes [7]. Ectosomes are rapidly generated at the plasma membrane: firstly cargoes assemble at the cytosolic face, and then differentiated membrane microdomains, marked by outward budding, appear at the cell surface and after vesicle fission, are rapidly released to the extracellular space [8,9]. The two types of vesicles cooperate in many physiological activities, and their mixture is critical in blood condensation, vessel formation, innate and acquired immunity, and synaptic transfer [8].

Exosomes could be secreted by dendritic cells, lymphocytes, epithelial cells, mesenchymal stem cells and cancer cells, and are ubiquitous in saliva, amniotic fluid, blood, urine, milk, cerebrospinal fluid, pleural effusion, ascites and other body fluids [10,11]. High-throughput research shows exosomes are biophysically equal to cytoplasm enclosed in a lipid bilayer and are rich in proteins, lipids, metabolites, and nucleic acids (Fig. 1) [12]. Exosomes vary compositionally among different origins of cells, but exosomes from different secretory cells share many protein components [13]. With the help of heat shock proteins (HSPs, *e.g.* HSP70 and HSP90) which promote peptide loading onto major histocompatible complexes (MHC-I, MHC-II), exosomes can get accustomed to the extracellular environment and induce the movement and cytolysis of natural killer cells to remove the diseased cells [14]. CD55, CD59, CD81, CD82 and Rab are involved in cell signaling transduction and cell membrane fusion [15–17]. Moreover, the nucleic acids of exosomes, such as DNA, microRNAs and mRNAs, are vital in

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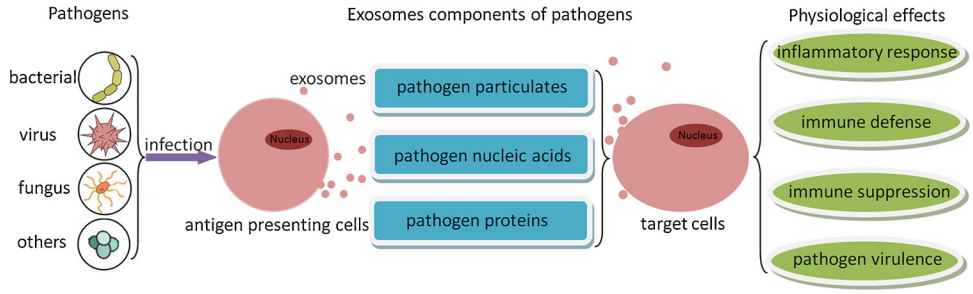

Fig. 1. Immune response modulated by exosomes in pathogenic infection. Exosomes modulate immune response by delivering pathogenic nucleic acids and proteins or even pathogen particles, and thereby affect many physiological activities, such as inflammatory response, immune defense/inhibition, and pathogen virulence.

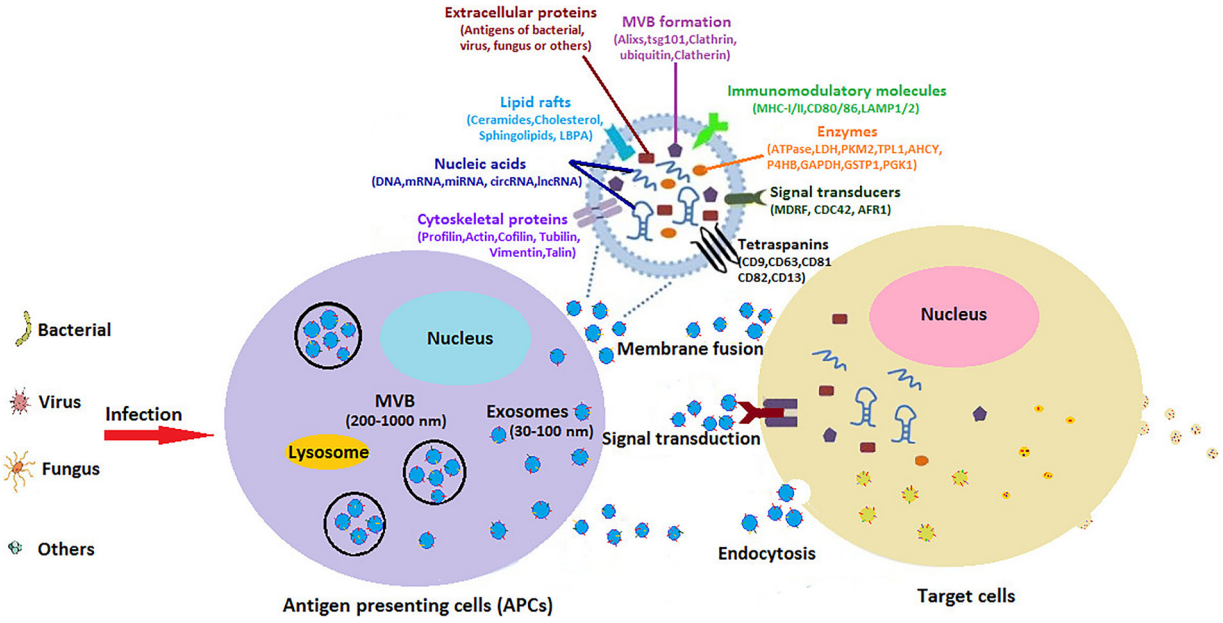

Fig. 2. Release, structure and components of exosomes derived by host cells. Once invading the hosts *in vivo*, the pathogens swallowed by antigen-presenting cells would be degraded by intracellular lysosomes, while antigen-carrying exosomes were released out to stimulate target cells, inducing specific immune response to get rid of pathogens. Exosomes are small membrane vesicles like plasma membranes, and their lipid bilayer membranes are composed of typical transmembrane proteins and receptors, and signal transducers factors of lipid raft-associated proteins. Immunomodulatory molecules assemble on the surfaces of exosomal membranes. Within the exosomal lumen are various proteins stabilizing and reserving exosomes structures, cytoskeletal proteins, enzymes, multivesicular body generation proteins, and other viral, bacterial and fungal proteins. Components of exosomes could be delivered from original cells to target cells in the microenvironment by genetic materials (*e.g.* DNA, mRNAs, miRNAs, cirRNAs and lncRNAs) and a variety of proteins relying on host cells.

cell signaling transduction and biological function regulation [16,18,19]. The DNA fragments of exosomes in peripheral blood are the potential biomarker of breast cancer [20]. The mRNAs and miRNAs from exosomes participate in protein synthesis and expression, respectively for example the miR-155 in exosomes is involved in the inflammatory response induced by *Helicobacter pylori* [21]. Long non-coding RNAs (lncRNAs) in exosomes could be a novel tumor biomarker for the screening and diagnosis at the early stage of GC [22]. Further research shows exosomes are involved in multifarious biological functions, such as cell signaling transduction, immune regulation, and promotion of tumor angiogenesis [23–25]. As an information messenger, exosomes deliver signal molecules and genetic information of tumor cells to nearby or distal normal, abnormal or immune cells, altering the phenotype or function of receptor cells and thereby the physiological effects of target cells, including inflammatory reactions, immune protection/inhibition and pathogen toxicity (Fig. 2) [26,27]. Experimental studies indicate pathogen infection exosomes could be used as adjuvant for vaccines or diagnostic biomarkers to develop immunotherapy. Since exosomes could carry bacterial antigens, viral proteins and other pathogenic factors to regulate immune systems, their influences on microbial infection and host cells have attracted growing attention. This review presents the recent advances of exosomes functions in pathogen infection.

2. Exosomes and pathogens infection

Fungi, bacteria and protozoa not only secrete some forms of microvesicles, including exosomes that are used by pathogens to spread infection and avoid the host immune system, but also together with viruses could stimulate exosomes production in host cells to regulate host immune responses [28,29]. Exosomes carrying various infectious agents by pathogens play a significant role in pathogenesis within hosts (Table 1). For instance, viral infections cause the formation and secretion of exosomes from host cells. The diverse proteins, lipids and nucleic acids in exosomes derived from pathogen cells or pathogen-infected host cells participate in several functions, such as spreading the infection *via* the epigenetic prevention of defensive mechanisms in the host, and triggering the transcription of pro-pathogen genes or limiting the infection through the presentation of microbial antigens into the host immune system [30]. In addition, exosomes containing proteins, RNAs *etc.* derived from pathogens infection host cells by inducing the activation of immune cells such as those related to the function of