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Conceptual Paper

The Potential Role of Exosomes in the Pathogenesis of Infectious Diseases and their Importance for Treatment and Prevention

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The field of exosome research is expanding, with a dramatic increase in publications in recent years. These small vesicles (30 - 100 nm) of endocytic origin were first proposed to function as a means for reticulocytes to eradicate the transferrin receptor then maturation in erythrocytes [1] and were later named exosomes. Exosomes are formed by inward budding of endosomes, production of multivesicular bodies and are released into the environment by fusion of multivesicular bodies with plasma membrane [2]. Since the first discovery of exosomes, a large range of cells has been shown to release these vesicles. Exosomes have also been detected in several biological fluids, including plasma, nasal wash fluid, saliva and [3-5] breast milk. Moreover, it has been shown that the content and function of exosomes depends on the cell of origin and the conditions under which they are produced. A variety of functions have been demons concentrated for exosomes, such as induction of tolerance against allergen [6], eradication of established tumors in mice [7] inhibition and activation of natural killer cells [8], promotion of differentiation in T [9] regulatory cells, stimulation of T [10] cell proliferation and induction of T cell apoptosis. It is important to note that the majority of studies using exosomes purified *in vitro* or from various biological fluids [11] and not *in vivo.*

Leishmaniasis is endemic in 98 countries, of which 72 are underdeveloped countries and are considered by the World Health Organization as a neglected tropical disease. More than 350 million people live in areas where parasite transmission is recurrent [12]. Each year, an estimated 1.5 to 2 million people develop a symptomatic disease and about 50,000 die, most of them children [13]. Climate change and population mobility can contribute to increased vector activity and, consequently, disease incidence [14]. In a new study published on the Cell Reports website [15], researchers described how key molecules, known as exosomes, can activate the infection mechanism of the leishmaniasis parasite in its hosts, such as humans or other mammals. These results could contribute to the identification of new targets for the development of vaccines and new diagnostic tools for leishmaniasis and other parasitic diseases.

The work of Atayde., *et al.* [15] is one of the first to demonstrate that a pathogen, such as the leishmaniasis parasite, harbored by a vector insect can release extracellular vesicles, the exosomes, which are an integral part of the cycle life of the parasite. Thus, bacteria and parasites transmitted while insects are feeding on blood could adopt a similar strategy to increase their infection rate. While in vitro experiments have established a large body of knowledge, the work of Atayde., *et al.* [15] is the first to provide a detailed description of their formation and release as a specific infectious agent in living organism. Using electron microscopy and proteomic analysis, they discovered that the parasite released exosomes into the gut of female sandflies and that while the insect was feeding on blood, the exosomes and parasite of leishmaniasis were transmitted to the host. They also discovered by working with mouse models, that once the parasite injected with its exosomes, they were able to advance the infection. Indeed, the inflammatory response, usually caused by the infection, as well as the number of parasites was increased. This discovery could pave the way for the development of new vaccines that would target the composition of exosomes and neutralize their ability to increase infection. Another interesting avenue would be to study the exosomes of other biting and blood-feeding insects, such as mosquitoes or black flies, in order to develop anti-allergy therapies to alleviate the skin inflammation that occurs after an insect bite.

The benefits of exosomes for immunotherapy lie in their ability to resist complement-mediated lysis [16] and their resistance to RNase, thereby promoting their stability in the body and protecting their nucleic acid content [17]. Added to this is their ability to modulate innate and adaptive immunity and their high immunostimulatory or immunosuppressive capacity [18]. Exosomes can also be used in vaccination [18]. The stability of the phenotypes and the presence of their functions following cryopreservation at -80°C (for six months) give these vesicles exceptional therapeutic characteristics. The demonstration of exosome vaccine properties against bacterial and parasitic infections has already been prov-

en. Indeed, exosomes derived from dendritic cells infected with *Toxoplasma gondii* or *Leshmania major* protect against these two parasites [19]. In contrast, exosomes secreted directly by *Leishmania major* and *L. donovani* inhibit immune responses in the body and promote parasite growth [20]. On the other hand, exosomes derived from macrophages infected with mycobacteria (*Mycobacterium tuberculosis, M. bovis*) and *Cryptococcus neoformans* induce the production of pro-inflammatory cytokines by naive dendritic cells and macrophages [21]. The properties of exosomes from macrophages infected with mycobacteria are similar to exosomes from macrophages infected with parasites such as *Toxoplasma gondii* [22]. Other parasites, such as *Leishmania*, secrete exosomes that contain soluble virulence factors, elongation factors-1 (EF-1a) and aldolase [23] as well as membrane factors of virulence (such as secreted acid phosphatase and metalloproteinase GP63) [20]. *Cryptococcus neoformans* secretes exosomes containing virulence-associated compounds including laccase, urease, glycosylceramides and glucuronoxylomannan capsular polysaccharide [24]. In addition, the exosomes of *C. neoformans* contain Hmp1 which is a membrane protein involved in cell adhesion [24].

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