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Exosomes, your body's answer to immune health

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Mesenchymal stromal cells (MSC) have a profound effect on the regulation of the immune system. MSCs show low expression of major histocompatibility complex (MHC)-II and costimulatory surface molecules that include CD40, CD40L, CD80 and CD86, indicating immunomodulatory properties (1). Interestingly, prior research indicated that MSCs are important immune modulators that exert their biological effects in a paracrine manner, involving secretion of exosomes. Exosomes have emerged as an important means for cellular communication through the transfer of proteins and genetic material between cells. Exosomes are a form of extracellular lipid vesicle that are usually 40–100 nm in diameter, have a density of 1.10–1.18 g/mL on sucrose gradients and contain exosome membrane-specific proteins such as CD9, CD63 and CD81 (2).

Many cell types have the ability to form exosomes through the inward budding of a lipid bilayer membrane. It was reported that exosomes can contain factors such as microRNAs (miRNAs) that maintain functionality after cellular transfer (3). These findings strongly support the immunomodulatory role of exosomes that originate from MSCs and their influence on host homeostasis. While the underlying mechanism(s) by which MSCs, exosomes and their secretory factors affect immunity is still lacking, Chen *et al.* (4) examined the immunomodulatory properties that MSC-derived exosomes exert on peripheral blood mononuclear cells (PBMCs), with special emphasis on the T-lymphocyte immune subset.

Exosomes have been reported to originate from many different cells types, thereby contributing to the wide array of biological functions observed (5). It has been theorized that exosomes are the paracrine effectors of MSCs and mimic important activities of their parental cell in a range of different models of disease. Coordinated inflammatory responses require intercellular communication in addition to immune cells such as dendritic cells (DCs) and T-lymphocytes, which are able to absorb and secrete exosomes. Several studies have reported that exosomes contain miRNAs that modulate the function of recipient cells such as those involved in cancer, heart disease (6) and dysregulated inflammatory states such as sepsis (7). MSC-derived exosomes exert various biological functions that include multi-lineage differentiation, cytokine(s) secretion, cellular proliferation and immunomodulation. Therefore MSC-derived exosomes are attractive as potential therapeutic agents.

In their study Chen *et al.*, reported on the immunomodulatory effects of MSC-derived exosomes towards PBMCs and especially, T-cells (4). MSCs were validated by their capacity to differentiate into multi-lineage cell types and possessed the typical mesenchymal markers according to flow cytometry. Exosomes generated from MSCs were isolated and identified via transmission electron microscopy, size distribution and content of exosome-specific proteins CD9, CD63 and CD81 by Western blot. MSC-derived exosomes were found to suppress T-cell activation and help maintain immune homeostasis.

PBMCs were stimulated with a range of concentrations of MSC-derived exosomes, and the ratio of CD4+/CD25+/CD127^{low} regulatory T-cells increased along with the expression of cytotoxic T lymphocyte-associated molecule-4 (CTLA-4), a negative regulator of T-cells. Previous studies had shown that MSC-derived exosomes promoted cellular proliferation (5) and indoleamine 2,3-dioxygenase (IDO) activity, but this study reported that proliferation and IDO activity was unaffected (8). Additionally in this study (4), apoptosis was found to be upregulated in both PBMCs and CD3+ T cells but not in prior studies (8). It should be noted that these discrepancies might be due to the different components that are carried within different types of exosomes or the underlying complexity that differentiates MSCs from MSC-derived exosomes and thus may significantly affect biological activities.

Of interest was the shift in cytokine profile generated by MSC-derived exosomes. Chen *et al.* (4) found significant inhibition of the pro-inflammatory cytokines, IL1β and TNFα but enhancement of the expression of the anti-inflammatory cytokine, TGFβ. This cytokine profile mimics the immunomodulatory effects of MSCs (5,6,9). These findings thus support a secretory mechanism by which MSCs might export exosomes-associated factors to the surrounding environment. The authors also reported that exposing CD4+ T-lymphocytes to MSC-derived exosomes increased the population of Th2 cells while also limiting the Th1 and Th17 T-cell subsets. They proposed that Th1 cells might differentiate into Th2 cells; however since only a single surface marker was used to distinguish these subsets, the heterogeneity and plasticity of T-cell populations cannot be fully addressed (10). Further identification of the T helper cell subsets might provide more conclusive insights.

The key finding of Chen *et al.* (4) was the role that MSC-derived exosomes play in dampening the activation of T-cells, enriching regulatory T-cell populations and their activity. The findings of their study further support the notion that MSC-derived exosomes can promote and maintain a modulated immune state. Although the mechanism by which MSC-derived exosomes function is not completely understood, it would be beneficial to define the internal constituents of exosomes since the origin of the parent cell contributes to the resulting components found within (5). Although this study did not identify the components of exosomes that drove the observed immunomodulatory effects, other published studies have implicated miRNAs as functional effectors.

miRNAs are small non-coding RNAs with the ability to target genes and initiate an immune response. miRNAs are typically short, 18 to 22 nucleotides in length, highly conserved and regulate diverse aspects of development and physiology through RNA silencing and post-transcriptional regulation. Moreover, miRNA expression has been found to correlate with disease states (3,11). It has been widely reported that exosomes can transport miRNAs that are functional in recipient cells, thereby mediating cell-to-cell communication. Therefore, miRNAs might display a protective role in attenuating inflammation or modulating the immune response.

Systemic inflammatory diseases such as sepsis are usually triggered by infection and can lead to organ failure and death. Although the clinical definitions have been updated, there is still a great need for the general agreement of definitions and identification of the factors at play during early sepsis (12). The mortality of sepsis is more than 30%, typically targeting the very young and elderly (13), but there are currently a lack of efficacious treatments. Sepsis was originally considered as the dysregulated

response of the host to infection, resulting in elevated and sustained levels of cytokines and chemokines (14). Additional study of this disease state observed much more complexity than initially considered. Rather than a primarily predominant hyper-inflammatory state, host blood cells undergo cellular reprogramming (CR) leading to an inability to respond to danger signals (15,16). The need for improved outcomes in sepsis makes MSC-derived exosomes an attractive therapeutic agent to help regulate immune function. Many studies have reported the importance of exosomal miRNAs and their ability to communicate and regulate cellular functions, including immunity (7,11).

Wang *et al.* found that miR-223 plays a cardio-protective role by dampening the inflammatory expression of immune cells in a polymicrobial murine cecal ligation puncture (CLP) sepsis model. Another study had reported that miR-223 has the ability to limit the expression of inflammatory genes (17) and Wang *et al.* further explored the impact it had on immune cells during sepsis and ultimately how mortality was affected. The study found that exosomes released from wildtype MSCs conferred survival to CLP mice while exosomes from miR-223 knockout MSCs proved detrimental. Thus, the lack of miR-223 within exosomes resulted in sepsis-induced heart failure, inflammation and death, while miR-223-containing exosomes attenuated the inflammatory response and minimized morality. These immune modulatory properties of MSC-derived exosomes are thus consistent with the findings by Chen *et al.* (4).

Altogether, these findings strongly implicate exosomes as a crucial component in modulating the immune system during a variety of different physiological perturbations. Therefore, the potential importance of exosomes and the significant roles they exercise in cellular communication necessitates further studies to clarify their mechanism(s) of action.

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