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Commentary: It's time for exosomes to get the limelight in lung transplant

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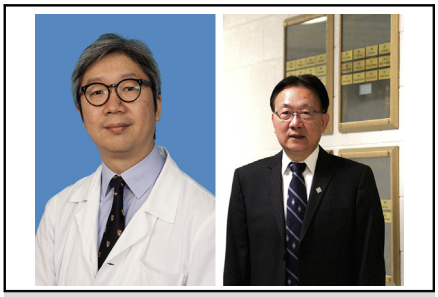

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CENTRAL MESSAGE

Exosome-based allorecognition pathways seem to be a missing link between innate and adaptive immunity and the development of CLAD. Exosomes might be potential biomarkers and targets of therapy for CLAD.

Lung transplant (LTx) recipients have the worst outcomes among all those receiving solid organ transplants, with 50% of recipients developing chronic lung allograft dysfunction (CLAD).[1] Understanding the immunology of LTx is an important step toward improving these outcomes. In this issue of the *Journal*, Hwang and colleagues[2] reviewed the potential role of exosome-based allorecognition pathways in LTx rejection, which seems to be a missing link between the innate and adaptive immunity and the development of CLAD.

The term exosome was first used by Johnstone and colleagues[3] in 1987 to describe sacs filled with smaller vesicles in maturing reticulocytes. Previously, exosomes had been regarded as a waste disposal mechanism. They are now understood to play important intercellular communication roles in normal physiology, such as reproduction and development,[4] immune modulation,[5] skin pigmentation,[6] and modulation of host defenses against pathogens.[7] In pathologic states, exosomes have been shown to be involved in neurologic diseases,[8] cardiomyocyte hypertrophy,[9] and cancer cell motility.[10]

In the review by Hwang and colleagues,[2] important preclinical models of skin and heart transplant were cited to show alloreactive T-cell responses are initiated by donor exosomes, instead of passenger leucocytes, as previously accepted.[11-13] New concepts, such as allo-exo-antigen, its production, and recognition pathways (direct, indirect, semidirect, and innate allo-exo-recognition), were introduced. These immunologic terms could be new to many thoracic and cardiovascular surgeons. However, understanding these new concepts could help us to develop new knowledge in the clinical LTx setting.

Exosomes have been implicated in the development of LTx rejection. The RNA profiles of exosomes extracted from bronchoalveolar lavage fluid from LTx recipients with acute rejection showed an inflammatory response, with signals of both innate and adaptive immune activation.[14] The serum and bronchoalveolar lavage fluid of LTx recipients with acute rejection or bronchiolitis obliterans syndrome, the exosomes contained donor human leukocyte antigens HLA and self-antigens (SAgs). These were not seen in stable LTx recipients.[15] Circulating exosomes

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isolated from LTx recipients with a diagnosis of respiratory viral infections contained lung SAgs, viral antigens, and 20S proteasome, and when these exosomes were given to mice, the mice elicited immune responses to lung SAgs that resulted in the development of CLAD.[16]

In LTx recipients, exosomes containing SAgs and collagen V were detected in the serum 3 months before clinical acute rejection and 6 months before the clinical development of bronchiolitis obliterans syndrome,[15] supporting their potential role as biomarkers of chronic rejection, although this requires further validation. Another line of investigation proposed by the Arizona group is blockage of exosome formation and release by pharmacologic agents during ex vivo lung perfusion to improve LTx outcomes.[17]

In the past decade, an explosion has occurred in exosome-related research across many fields. As our knowledge of the mechanism of alloimmune responses mediated by exosomes accumulate, a whole new area of clinical translation will likely open up, leading to improved outcomes for LTx recipients.

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