Commentary: Promising future solution for unmet needs in lung transplantation

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Central Message

Many issues hamper long-term survival in lung transplantation. Exosomes secreted in lung transplant recipients might be an important clue toward solving unmet needs in lung transplantation.

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Lung transplantation has been established worldwide as the final treatment option for severe respiratory failure, saving the lives of many severely ill patients. The 5-year survival is approximately 50%, however, and early mortality exists despite an occurrence rate of less than 10%.¹ Ischemia-reperfusion injury causes primary graft dysfunction (PGD), a major reason for early death after lung transplantation. Alloantibodies emerge after ischemia-reperfusion injury, and ischemia-reperfusion injury becomes a risk factor for chronic lung allograft dysfunction, a main reason for late death after transplantation. Other issues, such as PGD, acute rejection, donor-specific antibody, chronic lung allograft dysfunction including bronchiolitis obliterans syndrome (BOS), and restrictive allograft syndrome, remain unsolved. Recently, several techniques, including ex vivo lung perfusion and solid-phase antibody screening with identification of single antigens, have been developed and applied widely clinically to solve these complex, multifaceted issues.²

Mohanakumar and colleagues³ are to be congratulated for their interesting proposal in this issue of the *Journal* that PGD, acute rejection, donor-specific antibody, and BOS can induce and release exosomes into the circulation, which may play a role in inducing rejection. They have tried to prove this unique idea with multiple publications, including basic research.³⁻⁵ They have reported observational data sustaining their hypothesis, although they have not proved causality. Nevertheless, their theory could provide physicians and researchers in lung transplantation with meaningful and promising evidence to improve survival after lung transplant. It is hoped that Mohanakumar and colleagues further expand their study from the current preliminary and retrospective investigation³ to a more reliable prospective one. For example, the timing of the samples taken in relation to specific events should be described in more detail. Samples other than blood, such as exhaled air, sputum, and bronchoalveolar lavage fluid might be investigated. Moreover,

it might be interesting to investigate whether there are linear or other associations with PGD grades other than the binary PGD grade 0 versus grade 3. With chronic lung allograft dysfunction, restrictive allograft syndrome as well as BOS should be considered, because the restrictive allograft syndrome phenotype is known to be associated with worse survival than the BOS phenotype.

Although recently exosomes have been investigated in the field of transplantation, few reports have described the characteristics of exosomes in body fluids secreted by lung transplant recipients, including blood and bronchoalveolar lavage fluid. It is therefore still uncertain whether exosomes are induced by or the exosomes themselves cause injury in lung transplantation. Further studies are needed in the future.

According to the latest International Society for Heart and Lung Transplantation registry report, the survival curve after lung transplantation between 1999 and 2008 drastically improved in comparison with that between 1990 and 1998, but the survival curve between 2009 and 2016 did not improve in comparison with that between 1999 and 2008.¹ Further research by Mohanakumar and colleagues³ might provide valuable clues to solve these unmet needs and complex issues related to survival after lung transplantation.

In summary, Mohanakumar and colleagues³ showed preliminary observational data indicating that PGD, acute

rejection, and BOS might be mediated by exosomes, although the mechanism has not been proved.

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