Novel effect of rapamycin on experimental obliterative bronchiolitis

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Despite advancements in immunosuppressive regimens, chronic allograft rejection remains a significant challenge in lung transplantation. The hallmark feature of chronic rejection, bronchiolitis obliterans (BO), clinically manifests as a progressive decline in forced expiratory volume in 1 second and is associated with decreased graft and patient survival. The mammalian target of rapamycin (mTOR) inhibitor, rapamycin, has been described as a potential therapy for BO,¹ although its mechanism of action is incompletely understood. One likely mechanism is a decrease in proinflammatory cell (ie, fibrocyte, effector B-cell, and T-cell) infiltration.²

In this issue of the *Journal*, Zhao and colleagues³ nicely describe a novel mechanism of action for rapamycin in the prevention of BO—infiltration of regulatory B-cells (in addition to regulatory T-cells). This intriguing finding expands upon a paradigm suggesting a bipolarity of immune cells whereby similar cell types can exhibit either pro- or anti-inflammatory phenotypes. Regulatory B-cells, the authors report, secrete anti-inflammatory cytokines such as interleukin-10 and transforming growth factor β 1, which may be responsible for the recruitment of regulatory T-cells and the attenuation of BO.

Exactly how rapamycin achieves this end result is not completely known. A well-described mechanism of rapamycin is that it binds FK-506, which then blocks mTOR, leading to gap 1-synthesis phase cell cycle arrest and decreased B- and T-cell proliferation. Thus, the decrease in infiltrative fibroblasts and effector B- and T-cells makes rational sense. However, the mechanism for the increased infiltration of regulatory anti-inflammatory B- and T-cells with mTOR inhibition is poorly understood, although other authors have described it as well.^{4,5}

Zhao and colleagues³ correctly point out the limitations of the murine tracheal transplantation model used in this study, because BO is a disease process of the small airways and not large central airways. However, this model does display some important features of BO and currently represents 1 of the most reliable and reproducible models available.⁶ Regardless of this limitation, the findings are

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Central Message

A novel immunomodulatory effect of rapamycin protects against experimental obliterative bronchiolitis.

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important and intriguing and add merit to the evolving understanding of BO. Importantly, this article also sets the stage for future studies to elucidate a more detailed mechanistic understanding of how mTOR inhibition leads to regulatory B- and T-cell infiltration and the precise role of regulatory B- and T-cells in attenuation of BO.

A final point worth considering is the safety profile of rapamycin in patients undergoing lung transplant. There is a reported,⁷ and even late,⁸ incidence of anastomotic dehiscence with rapamycin use, and currently many transplant surgeons consider the drug to be contraindicated in the weeks to months following transplantation. Thus, the optimal timing of administration needs consideration. Additionally, rapamycin is poorly tolerated by some patients due to side effects, including pulmonary toxicity, thrombocytopenia, anemia, and wound complications.⁹

Zhao and colleagues³ have thoughtfully demonstrated a novel mechanism of rapamycin in the prevention of BO. However, perhaps the most important message—more so than the specific use of rapamycin—is the exploitative potential of regulatory B- and T-cells in BO. Understanding the mechanisms of regulatory cellular infiltration may ultimately drive improved prognostics and therapeutic options for lung transplant recipients.

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