Role of Complement Activation in Obliterative Bronchiolitis Post Lung Transplantation

Obliterative bronchiolitis (OB) is the leading cause of death post lung transplantation. This process involves IL-17-regulated autoimmunity to type V collagen and alloimmunity which could be enhanced by complement activation. However, the specific role of complement activation in lung allograft pathology, IL-17 production, and OB are unknown. The current study examines the role of complement activation in OB. Complement regulatory proteins-CRP (CD55, CD46, Crry/CD46) expression were down regulated in human and murine OB; and C3a, a marker of complement activation, was upregulated locally. IL-17 differentially suppressed Crry expression in airway epithelial cells in vitro. Neutralizing IL-17 recovered CRP expression in murine lung allografts and abrogated local C3a production. Exogenous C3a enhanced IL-17 production from alloantigen or autoantigen (type V collagen)-reactive lymphocytes. Systemically neutralizing C5 abrogated the development of OB, reduced acute rejection severity, resulted in lower systemic and local levels of C3a and C5a, recovered CRP expression, and diminished systemic IL-17 and IL-6 levels. These data show that OB induction is in part complement dependent due to IL-17-mediated down regulation of CRPs on airway epithelium. C3a and IL-17 are part of a feed forward loop that may enhance CRP down regulation suggesting that complement blockade could be a therapeutic strategy for OB.

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