Despite advances in immunosuppression over the last three decades, long-term kidney transplant survival is suboptimal, and mechanisms of late graft injury are incompletely understood. There remains a need for identifying and validating biomarkers capable of accurately stratifying patients into those at high versus low risk for developing late kidney allograft failure. While donor-reactive effector T cells (Teff) are recognized as crucial mediators of allograft injury and regulatory T cells (Treg) suppress Teff and protect against transplant injury, increasing evidence supports a multifaceted role for B cells in driving and regulating allograft injury as well.

One traditionally recognized function of B cells and their plasma cell progeny is that they produce donor-specific anti-HLA antibodies, which can contribute to graft injury. B cells can also process and present donor antigens to alloreactive T cells, thereby amplifying T cell–mediated damage to the transplanted organ. B cells are commonly present in transplant biopsy specimens with acute rejection, and molecular analyses have shown strong correlations between rejection and B cell–specific gene products, indirectly supporting a pathogenic role for B cells in human allograft injury.

On the other hand, multiple studies in mouse models of autoimmune disease and transplant rejection have shown that subsets of B cells can exhibit immunoregulatory properties and that these regulatory B cells (Breg) function by directly inhibiting pathogenic Teff and by facilitating induction of Treg, in part by producing the immune-suppressive cytokine IL-10.

In humans, molecular analyses of cellular RNA from blood and urine in two distinct populations of operationally tolerant kidney transplant patients who voluntarily withdrew from immunosuppression implicated B cell–derived gene products as involved in the tolerant state. Furthermore, B-cell production of IL-10, as well as plasma cell propensity for apoptosis, differs in operationally tolerant patients versus those with stable graft function on immunosuppression, supporting the concept that IL-10–secreting B cells may be protective in transplant recipients. Nonetheless, no studies have directly documented that Breg are present in the periphery of kidney transplant recipients receiving immunosuppression, and there is essentially no published evidence that Breg are relevant to transplant outcomes in this setting.

In this issue of JASN, Cherukuri and colleagues begin to fill this gap in knowledge by providing evidence that a subset of CD27\textsuperscript{neg}CD4\textsuperscript{hi}CD38\textsuperscript{hi} TrB cells produce the anti-inflammatory cytokine IL-10, as well as the proinflammatory cytokine TNF-α. They further showed that IL-10–secreting TrB can suppress T helper cell 1 cytokine producing Teff responses in vitro. Interestingly, concomitant production of TNF-α by the B cells overrides this inhibitory function, indicative of counter-regulatory mechanisms that could result in pro-versus anti-inflammatory outcomes dependent on the relative production of the two cytokines. The factors that guide B-cell production of IL-10 versus TNF-α, and whether
the IL-10–producing B cells are linked to production and/or stability of suppressive Treg, are important issues still to be addressed.

In addition to identifying Breg in transplant recipients and providing mechanisms to account for why some subsets of B cells can be suppressive while others are not, the results raise the possibility that quantifying the ratio of IL-10:TNF-α within TrB could be clinically informative as a biomarker for transplant outcome. To begin to address this, Cherukuri and colleagues correlated the ratio of IL-10:TNF-α in peripheral TrB from kidney graft recipients with transplant outcomes. Using an initial cross-sectional analysis of 88 recipients, the authors found lower IL-10:TNF-α ratios (driven by increased TNF-α expression) in TrB from recipients with rejection compared with those with “stable” graft function (defined as stable creatinine and absence of proteinuria). Consistent with findings from normal volunteers, TrB with higher IL-10:TNF-α ratios obtained from recipients with stable graft function inhibited T helper cell 1 Teff in vitro, while TrB with lower IL-10:TNF-α ratios, isolated from recipients with rejection, did not. In a subsequent longitudinal analysis of 44 kidney transplant recipients with graft dysfunction (n=44), the authors observed that a lower TrB IL-10:TNF-α ratio correlated with future, inferior 3-year graft outcomes. The utility of the TrB IL-10:TNF-α ratio as a predictive and clinically useful biomarker for risk-stratifying kidney (among other organ) transplant recipients must be validated using multicenter, prospective study designs, and accounting for clinical risk factors known to be associated with rejection. Moreover, as B-cell depletion strategies are being tested for clinical efficacy, it is essential to determine how such interventions affect IL-10–secreting and TNF-α–secreting TrB subsets, and how any detected changes correlate with clinical outcomes.

Ongoing efforts by multiple research teams to elucidate and substantiate the role of B cells in transplantation, beyond their known function as antibody-producing lymphocytes, are likely to continue to yield novel insights into basic immune mechanisms and to aid in the development of reproducible biomarkers for transplant outcome. The manuscript by Cherukuri et al. in this issue of JASN represents one step forward in this essential process.

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DISCLOSURES

None.

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