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B Cells in Transplantation: of rat, mouse and man

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Fifty-five years ago progress at several forefronts of immunology brought what seemed an epiphany that shaped the field of immunology for decades that followed. A search of longstanding for the anatomic origin of immunity had shown lymphocytes to be the cellular source of adaptive immunity but the source of lymphocytes was uncertain until Bruce Glick found that eradication of the bursa of Fabricius in newly hatched chickens blocked production of antibodies (1957) and Jacques Miller found that surgical removal of the thymus in newborn mice temporarily prevented rejection of skin allografts (1961). Whether these organs or their equivalents functioned in series or in parallel and whether functions seen in 1 species would apply to others, and especially to people was not clear. An answer to the first question came quickly when Szenberg and Warner in Melbourne (1962) and Cooper and Good in Minneapolis (1966) found that the bursa and thymus generate functionally distinct lymphocytes the former producing antibodies the later mediating graft-versus host-reactions and graft rejection. This anatomic and functional dichotomy led to the division of immunology into humoral immunity investigated by B cell people and cellular immunity by T cell people, a segregation that persists despite the discoveries that the protein products of the “immune response” genes that govern Ab production actually do so by presenting antigen to T cells that in turn “help” and regulate antibody responses, that T cell-antigen-receptor diversification in the thymus and periphery depends on diversification of immunoglobulin, the development of lymphoid tissues needed for T cells to encounter antigens and the regulation of T cell responses depend on B cells¹. But, which unifying observations in mouse and other species can be applied in people remains unclear.

A new model system reported by Panzer and colleagues² might help to address that question and in doing so help to reformulate lymphocyte biology. Panzer and colleagues asked whether and how B cells contribute to the early events after organ transplantation and did so using a new rat model rather than using established mouse models. Un-manipulated B cell-deficient mice reject organ allografts as quickly as wild type (WT) mice^{3,4}; however, transplants in B cell- and T cell-deficient mice suffer far less ischemia-reperfusion and early dysfunction thought to be caused by natural antibodies and complement⁵. To pursue this query further, the authors performed kidney transplants in B cell-deficient and WT rats and compared the function and pathology of kidney allografts on the 7th postoperative day.

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The gene targeted rats were probably not fully B cell deficient because targeting of mu heavy chain exons does not preclude generation of some B cells capable of producing IgG or IgA (and indeed some IgG-producing cells were detected by ELISPOT). The presence of some B cells however probably allowed lymphoid organogenesis and T cell development to occur ¹, without which some might question whether absence of B cells or aberrant T cells could explain whatever differences in outcome. Three clear and compelling findings emerged.

All transplants, 6 in WT and 5 in B cell-deficient rats, exhibited substantial early dysfunction. Transplants in WT mice had C4d deposits and more interstitial inflammation; B cell-deficient rats had increased expression of IL-10 mRNA in the spleen. Whether the early C4d and inflammation in WT and IL-10 in mutant rats will be found to presage rejection or absence thereof at later times remains to be seen, but, clearly none of these differences impacted on graft function during the first week after transplantation. These observations would seem to align with clinical trials revealing B cell depletion has no evident impact on the frequency or severity of early graft dysfunction ⁶.

In some mouse models, however, B cell (and T cell) deficiency protects against ischemia-reperfusion injury, in part by eliminating natural IgM, the binding of which to damaged cells activates complement ^{5,7}. In other mouse models, B cells and natural antibodies protect against or repair injury ^{8,9}. This bifurcated impact of natural antibodies could reflect differences concentration or specificity, among other possibilities ¹⁰. But, the obvious differences in availability of B cells and natural IgM, and corresponding differences in C4d and inflammation had no discernable impact on graft function in rats.

The absence of impact of natural antibodies in rat and man might reflect the striking of a perfect balance between the pathogenic and protective properties. However, the relatively limited variation in outcomes in Panzer's rats leads us to favor another explanation - that mouse on the one hand and rat and man on the other might differ in susceptibility to complement. Because complement system of mice is notoriously feeble, the complement system of rats and humans is robust ¹¹, we postulate the baseline and induced resistance to complement ¹² is less robust in mice than in rats and humans. Such differences would explain the pronounced impact of natural IgM in IRI in mouse and evidently minimal impact in rat ² and man ⁶. For the study of antibodies and complement in early graft dysfunction, therefore, rats may better approximate clinical transplantation.

Another consequence of the more robust complement system of rats however could be a greater impact of complement on cell-mediated immunity. Products of complement activation, including C5a, C3a and, as we recently showed, C3d ¹³ amplify and hasten cell mediated immunity and increase effector responses by increasing antigen presentation, effacing checkpoint inhibition and depleting regulatory cells. It might thus be the robust complement system of rats that compelled Panzer et al ² to administer cyclosporine to recipients to prevent early cellular rejection. Mice do not experience early cellular rejection of organ transplants; indeed, 70% of murine kidney allografts in untreated recipients escape destruction by acute cellular rejection ¹⁴. Which species then, mouse or rat, better represents clinical transplantation?

Yet unclear is the significance of the higher levels of IL-10 in the periphery of B cell-deficient renal allograft recipients. IL-10 mRNA can be found in the blood and spleen in relation to alloimmunity, and if that explains the small difference between experimental and control recipients we might wonder whether the B cell deficient rats are belatedly developing T cell responses. The graft histology suggests otherwise. More interesting to us is the possibility that B cells that bypassed expression of μ , perhaps B cells expressing IgD, could produce IL-10. If that is eventually found, the authors will have discovered a novel pathway to B cell regulation of T cell responses. Regardless of the answer, we eagerly look forward to what will follow on the present report, including the merger of B cell and T cell biology and migration of a broader concept of lymphocyte biology to the center of the stage of immunology.

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Abbreviation used

WT	wild type
IRI	ischemia-reperfusion injury

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