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Review

The coin toss of B cells in rejection and tolerance: Danger versus defense☆

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ABSTRACT

Transplantation is the preferred therapy for the end stage organ disease. Since the introduction of organ transplantation into medical practice in 1953 [1], significant progress has been achieved in patient and graft survival rates due to improvements in surgical techniques and more targeted immunosuppressive medications [2]. Nevertheless, current gaps in the management of the transplant patient stem from an incomplete understanding about the heterogeneity of the injury response in organ transplantation, at different rates and different time points after transplantation, as well as our inability to monitor the immunologic threshold of risk versus safety in each individual patient. Recent advances in immunology/transplantation biology with the advent of high throughput "omic" assays such as gene microarrays, proteomics, metabolomics, antibiomics, chemical genomics and functional imaging with nanoparticles, offers us unique methods to interrogate and decipher the variability and unpredictability of the immune response in organ transplantation (Fig. 1) [3]. Recent studies using these applications [3–8] have uncovered a critical and pivotal role for specific B cell lineages in organ injury [9] and organ acceptance [10,11] (Fig. 2). The availability of specific therapies against some of these defined B cell populations provides for an exciting new field of B cell targeted manipulation that can both abrogate the allospecific injury response, as well as promote allospecific graft accommodation and health.

1. The dual role of B-cells in transplantation

1.1. Role of B cells in solid organ graft rejection

B cells have many possible mechanisms by which they can affect allograft survival, including antigen presentation, cytokine production, immune regulation, and differentiation into alloantibody-producing plasma cells. Numerous reports have highlighted the role of B-cells in acute cellular and humoral allograft rejection and have been reviewed by us recently in detail [12,13]. Essentially B cells, in the course of their lineage development, undergo changes in phenotypic surface markers and functionality. Characterizing the pivotal role of specific B cell lineages in organ injury and acute rejection has become the subject of many studies over the last decade. These studies have demonstrated the key mechanisms by which B cells can result in both aggravated cytotoxic, cell medicated acute rejection, as well as humoral, antibody mediated acute rejection. These disparate mechanistic roles of B cells in organ injury have been increasingly recognized and accepted and have spurred interest in targeted B cell therapies for mechanistically different acute rejection episodes (Figs. 1 and 2).

1.2. The role of early B cell lineages in cellular acute rejection-evidence from mice and men

Various lineages of B cells are being increasingly recognized as important players in the etiology of both acute and chronic graft rejections. The role of immature, chronically activated B cells as efficient antigen-presenting cells supporting recalcitrant cell-mediated graft rejection is being increasingly recognized. In the last years, early lineage $CD20^+$ B cells have been demonstrated in up to 53% of acute cellular renal allograft rejections, correlating with resistance to conventional treatment and poor graft outcome/graft loss [13]. Early B cell lineages may modulate T-cell immunity by different mechanisms. In experimental transplant models it has been shown that B cells present autoantigens to promote activation of T cells, modulate T cell differentiation and effector function by cytokines production (IL-2, IL-4, IL-6, IL-10, IL-12, IFNg, TNFa), co-stimulate T cells via CD40 and OX40L, ICOSL, 4-1BBL, CD70, and

Abbreviations: AHR, Acute humoral rejection; ACR, Acute cellular rejection; BAFF, B-cell activating factor; DSA, Donor specific antibody; HLA, Human leukocyte antigens; IL, Interleukin; IVIg, Intravenous immunoglobulin; MAC, Membrane attack complex; PC, Plasma cells; PP, Plasmapheresis.

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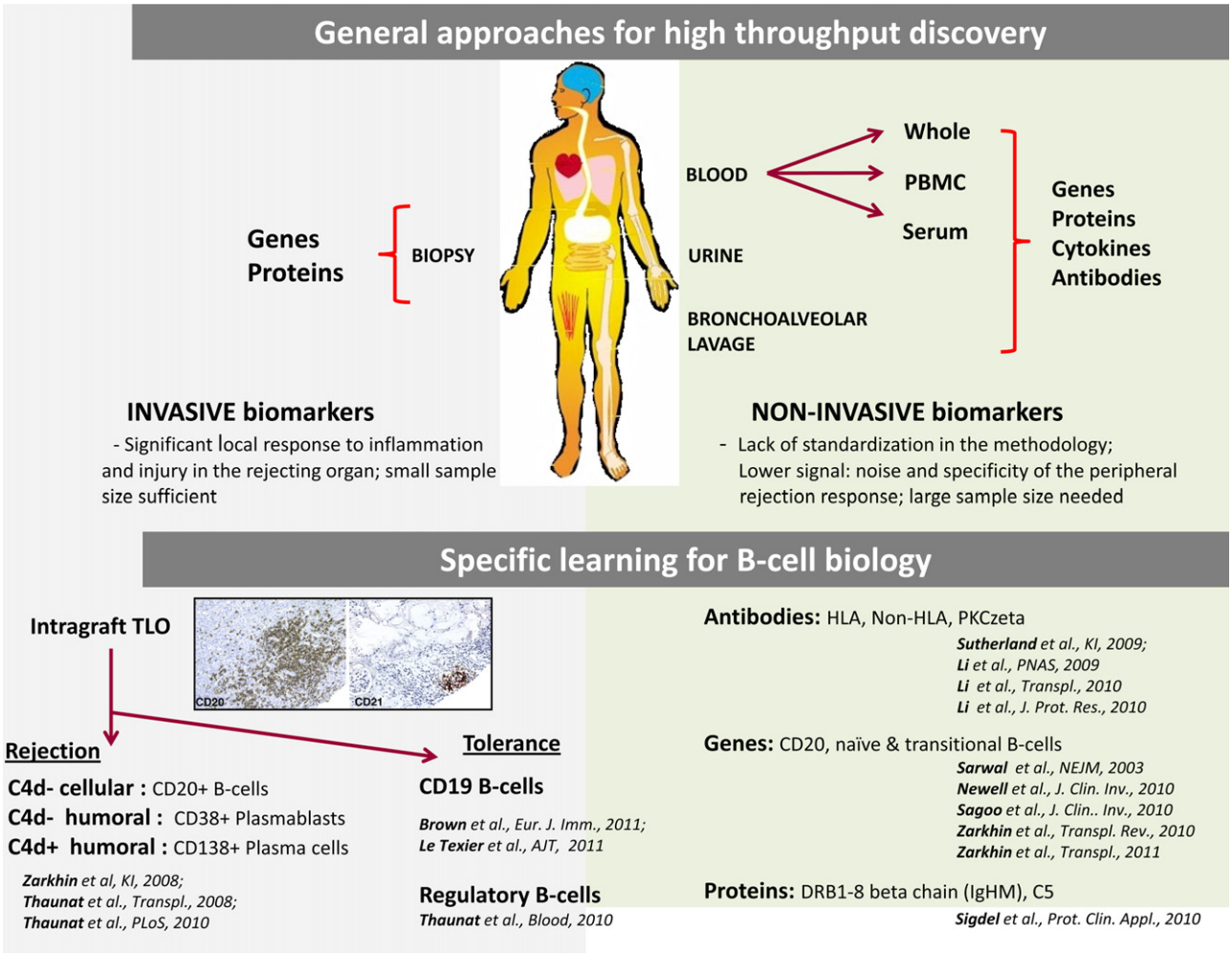

Fig. 1. High Throughput Discovery Methodologies that have been used to Understand B cell Biology.

promote differentiation of T cells to effector and memory T cells in ectopic lymphoid organs [13]. In 2003, using DNA microarrays in renal biopsy samples, our group have described gene-expression patterns associated with acute rejection and suggested at least three possible distinct subtypes of acute rejection that were marked by differences in immune activation and cellular proliferation, and further immunohistochemical stainings revealed a striking association between dense $CD20^{+}$ B-cell infiltrates and both clinical glucocorticoid resistance and graft loss [4]. Later, a pilot feasibility study of mRNA-based pancreas transplant biopsy stratification was performed, where the mRNAs expression of 32 genes, observed in renal transplant dysfunction, and 10 pancreas-specific genes were evaluated in 26 pancreas transplant biopsy specimens by quantitative real-time polymerase chain reaction using TaqMan Low Density Array technology and CD20/MS4A1 and CD3 mRNAs and proteins were reported potentially associated with pancreas allograft loss [14]. Subsequent experiments in our group and others have confirmed that these activated B cells may form extrafollicular plasmablasts, producing early, low affinity antibody or may enter the germinal center where they undergo somatic hypermutation and class switch recombination. Germinal center B cells with higher affinity for antigen are positively selected and then can differentiate into either memory B cells or plasma cells. B cells can produce various chemokines such as lymphotoxin-beta, CXCL13 and VEGF-A, driving lymphoid organ formation and lymphangiogenesis respectively, and thus play a role in controlling the development of these tertiary lymphoid organ structures within allografts.

1.3. The role of late B cell lineages in humoral, antibody mediated acute rejection

B-cell activation may occur directly in the graft. A small proportion of plasma cells arising from the germinal centers become established as long-lived plasma cells in the bone marrow. These plasma cells can reside within a number of limited niches, do not proliferate, and act as longterm antibody factories, producing IgG. Targeted areas of inflammation in the body, including the inflamed allograft in rejection injury, can provide niches for plasma cells. Whole genome gene expression profiling using microarray and proteomics enables researchers to detect the expression of thousands of genes simultaneously and leads to new insights into the heterogeneity, pathogenesis, classification, evolution, and prognosis of a wide range of immunogenic injuries in allograft transplants [15,16,18–20]. Recently, specific PBMC gene expression profiles have been reported in patients with antibody-mediated cardiac allograft rejection [21], suggesting that T-cell mediation may be required for all phases of the alloimmune response, whereas B-cell-mediated antibodies may play a role as the alloimmune response progresses, reflecting a complementary interaction between the innate and adaptive immune system.

1.4. Recovery of B-cell homeostasis after depletion of early B cell

Investigation of the effects of Rituximab (anti-CD20) on B-cell and B-cell-activating factor (BAFF) would better define the