Transplant Roundup

Progress in Immunosuppressive Agents for Solid-Organ Transplantation

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Immunosuppression is mandatory after organ transplantation, to prevent rejection of allografts. Discrete steps in the alloimmune responses that mediate rejection of transplanted organs have been discovered, enabling the development of immunosuppressive agents that can suppress specific immune responses, thus preventing rejection and minimizing adverse events.[1-4] All toxicities related to immunosuppression are dose-related, and combination therapies enable subtoxic doses of individual drugs.[5] Combination immunosuppression permits precise, personalized therapeutic approaches to transplant recipients and to patients who have immune-mediated diseases.[1-5]

Our comprehension of these issues began decades ago. The urgent need for skin grafting in World War II burn victims led to the conclusion that the reaction to a transplanted graft was an immunologic phenomenon. However, the differences between autologous (accepted as self) and allogeneic (rejected as foreign) grafts was poorly understood until the role of proteins encoded by genes in the major histocompatibility complex (specifically, human leukocyte antigen) became clear. By 1954, it was apparent that transplantation between identical twins should not cause rejection, because their cells shared an identical set of genes. On this basis, the first human kidney transplant was performed between identical twin brothers. Kidney transplants between unrelated individuals, however, had mixed results, despite intense immunosuppression in recipients. Only steroids and azathioprine were available, and this constrained progress in heart, liver, and lung transplantation.[1-3,5]

Upon discovering antigen processing and presentation by human leukocyte antigen molecules to T-cell receptors on T lymphocytes, we gained a better understanding of alloimmune responses in rejection and graft-versus-host disease (GVHD). Inhibitory therapies resulted from discovery of the molecular basis for the costimulation signal needed for robust T-cell activation and function.[2,3]

After soil samples were isolated for immunosuppressive agents, researchers developed cyclosporine and then tacrolimus, potent inhibitors of calcineurin that prevent production of interleukin-2 (IL-2), the principal mitogen in the proliferation of antigen-activated T-cell clones.[1] Soil samples from Easter Island later yielded sirolimus and everolimus, inhibitors of IL-2 signaling through the mechanistic target of rapamycin (mTOR).[3] Drug development programs undertaken to replace azathioprine as an antiproliferative agent produced mycophenolic acid and leflunomide, inhibitors of purine and pyrimidine synthesis, respectively. Characterization of the functions of unique cluster of differentiation (CD) molecules—expressed exclusively by different types of lymphocytes—facilitated production of therapeutic monoclonal antibodies (mAbs) to be directed against them.[1] Some mAbs can be used to eliminate rejection-causing T and B effector cells: two examples are muromonab (OKT3), directed against CD3 (expressed by all T cells); and alemtuzumab, directed against CD52 (expressed by all T and B cells). Basiliximab, an mAb directed against CD25 (IL-2R, expressed by all activated T cells), prevents IL-2 signaling through the mTOR pathway. Finally, mAbs against CD20 (expressed by all B cells) eliminate B cells while preserving antibody production by plasma cells.

Cytokines and chemokines, which are secreted by immune cells and by the target cells of rejection, direct the localization of inflammatory cells and intensify tis-

sue injury. Cytokines deliver their signals through Janus kinase–signal transducer and activator of transcription (JAK-STAT) proteins. Various JAK-STAT inhibitors of inflammation and injury are under development.[5] Agents to prevent trafficking of circulating effector cells into tissues include fingolimod, to prevent the release of T effector cells from lymph nodes; natalizumab, to inhibit integrin binding; and cenicriviroc, to inhibit the chemokine receptors that are necessary for leukocyte transendothelial migration into tissues.[1]

The recent discovery of preimplantation factor (PIF), a natural immunosuppressive and immunomodulating peptide that prevents maternal rejection of an allogeneic fetus, may lead to its development as an immunosuppressant without the risks of severe infections resulting from immune compromise.[6,7] Secreted by the embryo and later by the placenta, PIF creates maternal tolerance to an allogeneic embryo. In women who have autoimmune diseases, PIF often leads to spontaneous improvement during pregnancy and lowers the risk of postpartum flares. Results of PIF treatment in preclinical models of ovarian transplantation in baboons[6] and murine GVHD[7] have been promising.

The successful use of combination immunosuppressive therapies to prevent and treat acute rejection[1-5] has prompted a shift in focus from preventing rejection and accepting adverse sequelae to preventing rejection without severe adverse sequelae of immunosuppression. It now appears possible to tailor combinations of immunosuppressive drugs to minimize or prevent infection, malignancies, and chronic kidney disease, as well as cardiovascular complications associated with diabetes mellitus, hypertension, and hyperlipidemia. The discovery of accurate biomarkers of rejection will facilitate the development of personalized regimens that optimize the survival of allografts and patients while minimizing risks associated with immunosuppression.

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