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Development of immunosuppressants: Moving forward to the next generation

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Pharmacological immunosuppression enables successful organ transplantation. Patients receiving organ transplants are usually given immunosuppressants, which dramatically improve the short-term consequences of organ transplantation. However, patients are exposed to the detrimental effects of life-long continuous immunosuppression, including infection, cancer, and metabolic toxicity.

The current immunosuppressive therapies mainly block T cell activation. They target antigen-presentation (signal 1), costimulation (signal 2), and cytokine production (signal 3). However, the long-term transplant survival rates remain suboptimal, highlighting the need for additional approaches to control the immune responses.

This talk will focus on developing new therapeutics targeting regulatory T cells and innate immunity to establish transplantation tolerance: 1) small molecules promoting the generation of antigen-specific effector regulatory T cells, and 2) nanobiologics targeting myeloid cell activation to prevent inflammatory responses that drive graft rejection.

In addition, I will introduce a case of drug development targeting the aryl hydrocarbon receptor (AHR), which is a ligand-activated transcription factor. The AHR is activated by various small molecules originating in the diet, microorganisms, host metabolism, and xenobiotic toxic chemicals. Its activation by endogenous ligands such as tryptophan metabolites ligands counteracts the excessive inflammatory response. Accordingly, the administration of AHR ligands effectively inhibits inflammatory tissue reactions, particularly in the barrier organs. However, there are limitations to using AHR ligands as therapeutics because of their poor pharmacokinetics, low efficacy, and toxicity. Therefore, our research team developed a novel synthetic AHR agonist that prevents alloreactive immunopathology in mucosal organs after hematopoietic cell transplantation by inhibiting innate inflammation and promoting FoxP3+ regulatory T-cell differentiation. These results suggest that a specific AHR agonist may exert therapeutic activity against inflammatory responses that drive graft rejection.