Role of Innate Immunity in hematopoietic stem cell-mediated allograft tolerance

Reporting Period: Year 1

Recent studies conducted first in animals and subsequently confirmed in humans have shown that tolerance to solid organ transplants can be achieved using donor-derived hematopoietic stem cells (HSCs). HSCs can induce tolerance by embedding in the recipient’s thymus. Once in the thymus they cause the deletion or inhibition of recipient cells that would otherwise cause rejection of a transplanted organ from the same donor. The coexistence of donor and host hematopoietic cells is called mixed chimerism and as long as the donor cells remain in the host, an allograft from the donor can be accepted without the need for immunosuppression. Although many studies have shown that mixed chimerism can be obtained, donor tissue can still reject because the host responses to engrafted organs are not completely suppressed. Therefore, before HSC strategies can be widely used, additional refinements are needed to prevent activation of host responses. A logical approach, based on recent new information about the early activation events, involves targeting primitive receptors that are initial triggers of adaptive immunity – pattern recognition receptors (PRRs). Pattern recognition receptors have recently been linked to activation of HSCs because it is known that HSCs undergo massive expansion and migration in inflammation. Two families of PRRs have been identified in HSCs - toll-like receptors (TLRs) and NOD-like receptors (NLRs). TLRs reside on cell membranes and NLRs are found within the cells HSCs. TLR/NLR-induced expansion and differentiation of HSCs results in their differentiation into activated cells that trigger rejection of donor cells (i.e., chimeric donor cells that would otherwise ‘tolerate’ host T cells are rejected). The end result of the PRR-induced activation of HSCs is loss of mixed chimerism and graft rejection. We have already shown that targeted blockade of specific PRRs can prevent ischemia-mediated tissue injury, inflammatory responses to the tissue injury, and also prolong survival of highly immunogenic allografts. The overall objective of our project is to identify novel potential drug targets that promote HSC-mediated tolerance to transplanted solid organs. The idea is that signals mediated through PRRs interfere with HSC-mediated mixed chimerism and tolerance induction. We proposed to test our hypothesis in three interrelated aims. The first aim focused on testing the role of PRRs in the induction of tolerance. The second aim focused on the role of donor cells in the induction of host T cell unresponsiveness. The third aim focused on the role of HSC-mediated mixed chimerism on donor graft survival. The first year of funding has already led to some important initial findings that are setting the stage for our understanding the role of hematopoietic stem cell induced tolerance. We believe that many, unavoidable, signals are activated during the course of HSC harvest and transplantation and that some of these signals reduce the ability of the transplanted HSCs to engraft in the host. Our initial findings suggest that if some of these signals are blocked, HSC engraftment, and transplant tolerance, can be enhanced. We are currently testing our initial exciting findings and progressing on the second and third aims of the study.

Reporting Period: Year 2

During the past funding period several significant advances were made towards each of the three aims of the proposal. We found that innate immune receptors were critically important to engraftment of hematopoietic stem cells and we have begun to understand how engraftment is enhanced in the absence of some of these receptors. We also discovered important aspects of the biology of the KO cells and how they might confer better engraftment. Our ongoing studies are focused on the mechanistic factors that lead to enhanced hematopoietic stem cell engraftment in our model.

Reporting Period: Year 3

Significant progress was made in the three aims of this project. Most important was the finding that we could markedly improve engraftment of foreign hematopoietic stem cells by removing certain receptors of the innate immune system from the donor stem cells. We have pursued an understanding of how cells without these innate immune receptors can be better at engraftment. It appears that T cells lacking these receptors are less able to proliferate in response to the foreign antigens.
Role of Innate Immunity in hematopoietic stem cell-mediated allograft tolerance

Grant Type: Transplantation Immunology
Grant Number: RM1-01709

Project Objective: This proposal aims to test the hypothesis that signals mediated through pattern recognition receptors (PRRs) impair the development of HSC-mediated mixed hematopoietic chimerism and impair HSC-induced tolerance to solid organ transplants.

Investigator:

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Disease Focus: Blood Disorders
Human Stem Cell Use: Adult Stem Cell
Award Value: $1,705,554
Status: Closed
Application Title: Role of Innate Immunity in hematopoietic stem cell-mediated allograft tolerance

Public Abstract: The research proposed in this project has very high potential to identify new medications to boost the natural ability of stem cells to prevent rejection of transplanted organs. This is a very important goal, because patients that receive a life-saving transplanted organ must take toxic medications that increase their risk for cancer and serious infections.

Experimental clinical trials have recently shown that stem cells given to patients at the same time as they receive their transplanted organ can engraft in the patient and prevent rejection of the transplanted organ, without the need to take immunosuppressive medications. The problem though is that the stem cells don't last forever; they are eventually rejected by the patient's own immune system.

A promising target to prevent rejection of stem cells in patients is a group of primitive molecules that are receptors on stem cells, as well as many other cells in the body. These primitive receptors are called innate immune receptors and they provide the trigger for activation of a cascade of mechanisms that lead to rejection of the stem cells. If the trigger is not pulled, then the stem cells will not be rejected.

Therefore, our proposal focuses on how to block activation of the rejection cascade so that stem cells are able to engraft in the patient and prevent rejection of transplanted organs, without the life-long use of toxic medications.

We have extensive experience studying innate immune receptors and transplantation and therefore are poised to make significant advances in our understanding of how stem cells are rejected by signals that depend on innate immune receptors. Furthermore, once we identify which innate immune receptors are relevant, targeted rationale blockade of these receptors can be proposed.
**Statement of Benefit to California:** The proposed research will benefit the State of California and its residents by providing important knowledge about new ways to prevent rejection of transplanted organs. Currently, patients with transplanted organs must take life-long toxic medications to prevent rejection of their organs. This proposal will help develop ways to avoid the use of these toxic medications, while allowing life-saving organ transplants to survive in their new host. The use of stem cells in recipients of solid organ transplants is the first new breakthrough in decades for transplantation and therefore it is very important to try to optimize the use of stem cells to allow the survival of transplanted organs without toxic immunosuppressive medications.

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