

INTERVIEW about

Role for CCR5 in the function of regulatory T cells with

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What is known about the role of regulatory T cells during graft-versus-host disease?

Jonathan S Serody and Tim Moran: Several groups including ours have shown that the infusion of regulatory T cells with effector T cells can diminish or completely inhibit graft-versus-host disease in MHC mismatched transplantation using murine models. Initially, our collaborator Bruce Blazar demonstrated that regulatory T cells expanded in culture could inhibit GVHD across both a class II MHC and a completely MHC mismatched murine model(1). Following this our group along with that of Sam Strober that showed that regulatory T cells that expressed high levels of L-selectin

potently inhibited GVHD while those that expressed lower levels of L-selectin did not (2,3). Both phenotype of cells could inhibit T cell proliferation *in vitro* but migrated to different areas with L-selectin^{hi} regulatory T cells migrating to lymphoid tissue and L-selectin^{lo} regulatory T cells migrating to parenchymal organs. These data suggested that regulatory T cells inhibit GVHD by blocking T cell proliferation in lymphoid tissue. Thus, the current work is important in that it now shows that migration to both lymphoid tissue and parenchymal organs is critical in blocking GVHD (4).

Are any news about the C-C chemokine receptor 5?

Jonathan S Serody and Tim Moran: Previous investigators had shown that B cells, dendritic cells and macrophages generated the chemokine CCL4 (MIP-1 β) and that this led to the migration of regulatory T cells (5). Inhibiting CCL4 led to the generation of autoantibodies suggesting that CCL4-B cell, regulatory T cell interactions were important in controlling the production of these autoantibodies. Interestingly, we found that regulatory T cells migrated significantly to all of the ligands that bind to CCR5, however, unlike the work from Bystry et al

we found that regulatory T cells required activation via the T cell receptor to migrate to these ligands. Additionally, we show in the current manuscript that regulatory T cells migrate better to ligands that bind CCR5 compared to the migration of CD4⁺ effector cells. In our current work, we have found that the absence of CCR5 on regulatory T cells impaired their migration to the liver and lung during GVHD and that this led to enhanced GVHD at these sites and earlier lethality in a haploidentical mouse transplant model.

Why is CCR5 necessary for regulatory T cell function?

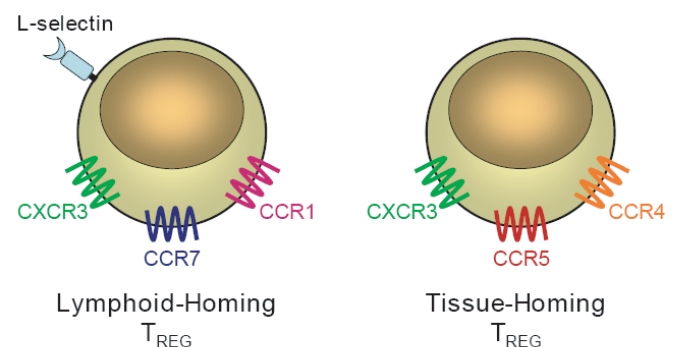
Jonathan S Serody and Tim Moran: Our work demonstrates that CCR5 is unre-

gulated on regulatory T cells after activation, which most likely occurs in lymphoid tissue. This upregulation is critical in allowing regulatory T cells to migrate out of lymphoid tissue to specific organs where GVHD occurs. Previously we have shown that activated T cells generate ligands that bind to CCR5 in these parenchymal organs. Thus, our data suggest that the expression of CCR5 by regulatory T cells is quite important in dampening immune responses in tissues where CCR5 ligands are expressed by previously activated effector T cells.

Are dendritic cells involved?

Jonathan S Serody and Tim Moran: At this time, we do not know if dendritic cells located in specific tissues are

critical in either the activation or inhibition of regulatory T cells at those sites.



REFERENCES

1. Taylor PA et al. Blood 99, 3493, 2002
2. Taylor PA et al. Blood 104, 3804, 2004
3. Ermann J et al. Blood 105, 2220, 2005
4. Wysocki CA et al. Blood 2005
5. Bystry RS et al. Nat Immunol 2, 1126, 2001