

## INTERVIEW about

Macrophages suppress  
T-cell activation

with

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## How can T-cells be activated?

**James E. Riggs:** The innate (nonspecific) and adaptive (specific) immune system intersect when antigen presenting cells (APCs) such as dendritic cells (DCs) and macrophages (Mφs) present peptide antigens to helper T lymphocytes in organized lymphoid tissue. Rather than recognizing intact, soluble proteins, the T cell receptor (TCR) binds peptide fragments associated with major histocompatibility complex (MHC) molecules. Mφs and DCs ingest protein antigens and process and present them in peptide form complexed with MHC molecules to promote T cell activation. This T cell- APC interaction repre-

sents a critical control point for the initiation of, and transition to, an adaptive immune response. In addition to TCR-MHC + peptide interaction, there are other receptor-ligand combinations that dictate whether activation or inactivation will result from APC-T cell contact (1). Although immunology textbooks emphasize activation as the result of APC-T cell interaction, there is a growing body of work that suggests that this interaction can temper immunity. This can be a good thing, *eg.*, turning off unnecessary responses, or a bad thing, *eg.*, preventing an immune response to cancer cells.

## How did you come to study macrophage suppression of T-cell activation?

**James E. Riggs:** With interests in B cell subpopulation biology, our laboratory was not studying Mφs. In these studies we compared B cells from the spleen (B2-subset-enriched) and peritoneal cavity (PerC) (B1-subset-enriched). We found that PerC cells failed to present a retroviral superantigen (SAg) to T cells. This was a mystery to us until we conducted co-culture experiments in which we found that the PerC cells actively suppressed the T cell activation normally induced by spleen B cells (2). Since sorted PerC B cells could present the SAg to T cells some other cell was responsible for the suppression witnessed in the PerC plus spleen cell co-culture studies (3). Subsequent experiments with mutant strains of mice, depletion and enrichment of PerC Mφs, and flow cytometric analyses of the cellular composition of the PerC led to the discovery that macrophages were responsible for this suppression (4).

## What is the role of interferon-gamma in macrophage-mediated suppression?

**James E. Riggs:** Our initial attempts to address the mechanism of suppression focused upon cytokines. We anticipated increased production of cytokines known for their immune-tempering properties such as IL-10 or TGF-β.

However, IFN-γ production was always high in these cultures so we tested for suppression with PerC Mφs from IFN-γ receptor knockout mice. These Mφs failed to suppress T cell activation. The literature in this area led us to the work of Andrew Mellor and David Munn who had earlier shown that Mφs, via expression of indole-

amine dioxygenase (IDO), suppress T cell activation by catabolizing tryptophan (5). We subsequently found that nitric oxide synthase (NOS) catabolizes arginine in these cultures. Thus, Mφs have several enzymes triggered by IFN-γ production that temper T cell activation by catabolizing particular amino acids.

What do you think is the *in vivo* biology of macrophage-mediated suppression?

**James E. Riggs:** We think that this aspect of Mφ function is essential for “housekeeping” in the body, *ie.*, cleaning up apoptotic debris in a noninflammatory fashion. Impairing this critical Mφ function is lethal during early development when significant tissue “grooming” or apoptosis is occurring (6). The quiescent differentiation state of these cells correlates with their non-inflammatory, housekeeping function. Historically, studies of Mφs have focused upon cells that have been activated by, or for, their isolation. Small numbers of activated Mφs are very effective APCs for T cells. There has been less study of “naïve” Mφs. Our results suggest that such cells can suppress T cell activation and that the Mφ:T ratio is a critical factor. This generates the ques-

tion as to where such ratios might exist in the body. It should be rare that Mφs, naïve or activated, represent a large proportion of the cells in any particular tissue. An important exception is in certain tumors, where up to 70% of the cells have been found to be Mφs (7). This represents an immune-suppressive microenvironment that correlates with the Mφ:T cell ratio evident in our cultures. How does this cellular imbalance get established? Were the Mφs initially summoned to a site with a high apoptotic burden? Was immunity stalled in this non-lymphoid tissue due to an imbalanced architecture for the proper initiation of adaptive immunity? These are key questions that we believe will be addressed by tumor immunotherapy researchers.

## Will this information lead to the development of novel immunotherapy strategies for tumors?

**James E. Riggs:** We certainly hope so! Characterization of the myeloid cells that suppress immunity in tumors continues to move forward. Significant progress is being made in understanding the costimulatory and coinhibitory receptor-ligand interactions between APCs and T cells (8). A comprehensive understanding of these cells and their molecular interactions will foster advances in reducing suppression and pro-

moting effector cell function within the tumor. The ability to promote host anti-tumor immunity without exposing the patient to toxic treatment regimens would represent a major advance in oncology.

## REFERENCES

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