Immune-Mediated Mechanisms of Phthisical and Non-Phthisical Intraocular Tumor Rejection

Terry Glenn Coursey, II, Ph.D.
The University of Texas Southwestern Medical Center at Dallas, 2011
Graduate School of Biomedical Sciences
Supervising Professor: Jerry Y. Niederkorn, Ph.D.

Date Available: 12/12/2011
Summer 2011
IMM
Bibliography: pp. 191-215

Keywords: eye; intraocular tumors; iNOS (Inducible nitric oxide synthase); IFN-8; macrophages; TNF-alpha; IL-17; CTL (Cytotoxic T lymphocytes)

Although intraocular tumors reside in an immunoprivileged site where immune responses are suppressed, some tumors are rejected nonetheless. An example of this is the syngeneic adenovirus-induced (Ad5E1) tumor model. Intraocular tumors are rejected in one of two pathways: one that maintains normal architecture and function of the eye and one that causes gross destruction leading to necrosis or phthisis. Ad5E1 tumor cell lines were created from single cell clones that are consistently rejected in a phthisical manner or non-phthisical manner.

The first objective sought to characterize non-phthisical intraocular tumor rejection. I demonstrated that this form of rejection is dependent on T cells. Rejection was also found to be dependent on M1 macrophages that mediate cytotoxicity; however, iNOS was not required. An unidentified soluble factor was determined to be responsible for macrophage-mediated killing.

My results indicated that T cells and M1 macrophages were required for phthisical rejection of intraocular Ad5E1 clone 2.1. In addition, in vitro inhibition of iNOS abolished most of the macrophage-mediated killing of the tumor cells, and in vivo results indicated that iNOS was essential for controlling the growth of the intraocular tumors. Studies in tumor necrosis factor (TNF)-deficient mice revealed that although TNF-alpha was not necessary for tumor rejection, it was required for phthisis. Thus, this model demonstrates that it is possible to modify the host's response such that the immune system eliminates the intraocular tumor while preserving the integrity of the eye.

The last aim sought to determine the mechanisms of IFN-gamma-independent tumor rejection. Although phthisically-rejected Ad5E1 tumors were not rejected when transplanted into the eyes of IFN-gamma KO mice, they were rejected following subcutaneous transplantation (SC). Thus, outside of the eye, Ad5E1 tumors elicit a form of tumor immunity that is IFN-gamma-independent. SC tumor rejection required IL-17, which was produced by CD4+ T cells in response to tumor antigens (TAs). Additionally, depletion of IL-17 decreased CTL activity against Ad5E1 tumor cells. However, this does not occur in the eye. IL-6 production within the eye is severely reduced, which is consistent with the failure to induce Th17 cells within the intraocular tumors. Therefore, IFN-gamma-independent tumor rejection is excluded from the eye and may represent a newly recognized form of ocular immune privilege.