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Cancer biology of human T cells: studies on growth factor production, activity and cell transformation

T cell Transformation by the Human T cell Leukemia Virus Type 1: The Human T-cell Leukemia Virus, HTLV-1, is the etiologic agent of Adult T cell Leukemia Lymphoma or ATL. This virus has also been implicated in Tropical Spastic Paraparesis or TSP, a degenerative disease of the central nervous system. This virus is endemic to several areas of the world and has recently been shown to be on the rise in the United States. It is important for us to understand how this virus causes disease. The work in my laboratory is involved in the study of how this virus causes transformation in normal T cells inducing ATL. Previous work with our colleague, Dr. Michael Nerenberg, has indicated that leukemic cells contain constitutively active JNK1/2 kinases. These kinases are required for the activation of the Jun and ATF transcription factors. Dr. Nerenberg hypothesized that these transcription factors, particularly ATF-2 which appears to be active in HTLV-1 infected cells, may be responsible for the transformed phenotype of leukemic cells. We are currently using a murine tumor-model system to evaluate the role of ATF-2 in HTLV-1-mediated carcinogenesis.

Interleukin 2 (IL-2) stimulation of primary and HTLV-1 infected T cells: The IL-2 growth hormone is the major growth factor for human T lymphocytes and controls both the success and the magnitude of normal immune responses. IL-2 promotes both the growth and survival of normal T cells rendered responsive to the growth factor. HTLV-1 transformed T cells, on the other hand, overcome their need for IL-2 and it is thought that this process is required for the development of leukemia because the transformed cells do not make their own IL-2. Interestingly, human T cells that are immortalized by Tax, the putative transforming protein of HTLV-1, will grow indefinitely in tissue culture if IL-2 is present but they never lose their dependence on exogenous growth factor. We now know that these cells require IL-2 to grow (progress through the cell cycle) but they do not need it for survival. Our hypothesis is that whatever IL-2 is required for in these cell lines is subverted or deregulated during the transformation process. Therefore, another emphasis of the laboratory is to characterize IL-2-dependent events, including signal transduction, gene expression and biologic consequences, in both normal and Tax-immortalized human T cells. These studies will provide not only a better understanding of the transformation of T cells by HTLV-1 but of IL-2-promoted growth and survival of normal T cells as well.

Mimicking natural products to develop novel cancer and immunosuppressive drugs: A new and exciting project in the laboratory is based on our recent observation that a novel protein discovered by our collaborator, Dr. William Wachsman, specifically inhibits the expression of the IL-2 gene in stimulated T cells. Our studies indicate that this small bZIP protein, called SNF, works by inhibiting the activity of a very important transcription factor called AP-1. AP-1 is made up of two proteins, called Fos and Jun, both of which are products of "protooncogenes", i.e. genes that when altered can cause cancer. We are currently studying the molecular mechanisms used by SNF to repress AP-1. When we know more about the action of this protein, we want to identify potential drugs that can mimic the activity of the protein in vivo. Because AP-1 is often implicated in the development of cancer, and the unregulated production of IL-2 is involved in both autoimmunity and tissue graft rejection, we hypothesize that our studies will lead to the identification of new drugs with low toxicity that have immunosuppressive and/or anti-cancer activities.

Representative Recent Publications:

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