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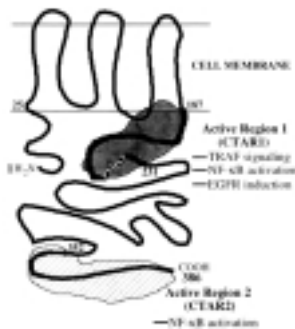
My laboratory investigates the role of the Epstein-Barr virus in the etiology of human disease. EBV is a ubiquitous infectious agent which is associated with specific malignancies including Burkitt's lymphoma, Hodgkin's lymphoma, and nasopharyngeal carcinoma (NPC) which develop with high incidence in endemic areas. EBV is etiologic for post-transplant lymphoma and also causes the AIDS-associated disease, hairy leukoplakia (HLP).

We have identified the genes which are expressed in NPC by cloning and sequencing cDNAs directly from tumor tissue. These studies have identified three viral genes which are consistently expressed and have identified a new family of transcripts which are expressed at particularly high levels in NPC tissue. These new mRNAs are intricately spliced and contain several new open reading frames that could potentially code for protein. We have shown that one of these open reading frames does encode a protein that is expressed at high levels in EBV associated cancers and is localized in the membrane fraction of the cell. We are investigating the functions of this gene using the two hybrid analysis in yeast cells.

The interaction of these genes and their effects on cellular gene expression is also an area of interest. We have determined that the p53 tumor suppressor gene is not mutated in primary NPC tissue or in post-transplant lymphomas. This lack of mutation suggests a lack of selection for mutation in EBV malignancies. We have recently shown that the EBV latent membrane protein 1 (LMP1) indirectly interferes with p53 function by inhibiting p53-mediated apoptosis. We have established three lineages of transgenic mice that express the LMP1 protein in B cells. These mice have increased development of lymphoma. In the lymphoma tissue, LMP1 is consistently expressed and the cellular oncogenes, c-myc, bcl-2, and A20 are detected at high levels. This suggests that activation of expression of these cellular genes is an important component of LMP1 mediated lymphomagenesis.

We have also shown that in epithelial cells, LMP1 induces expression of the epidermal growth factor. Genetic analysis has revealed that this induction is dependent on DNA sequences in LMP1 which interact with the cellular TRAF molecules that are the signalling molecules of the tumor necrosis factor family of receptors.

Future projects will continue to investigate the molecular properties of the viral proteins that are expressed in cancers associated with EBV. We hope that by identifying the viral genes expressed in diseased tissue and through the development of in vitro assays of biochemical functions and transgenic mice, we will unravel the biochemical processes through which the Epstein-Barr virus alters cell growth control.



Model depicting the molecular structures and locations of functional domains in LMP1. LMP1 contains a 24-amino-acid cytoplasmic amino terminus, a transmembrane hydrophobic domain, and a 200-amino-acid cytoplasmic carboxy terminus. The carboxy terminus contains the major signaling domains in LMP1. CTAR1 mediates interaction with the TRAFs, induces EGFR expression, and is the minor NF-κB-activating region; CTAR2 is the major NF-κB-activating region.

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