

Brian A. McCarthy

The Role of IL-10 in B-1 Malignancies

[This project will examine the proliferative and anti-apoptotic effects of IL-10 on B-1 Cell malignancies]

Chronic lymphocytic leukemia (CLL) is the most common cancer in the western world. The New Zealand Black (NZB) mouse strain has long been used as a model for CLL. CLL and malignancies of B-1 cells, a unique subset of B cells, are characterized by a progressive accumulation of malignant B cells, which are usually detected late in life. The expansion of a malignant clone is associated with not only sustained growth, but a failure to undergo programmed cell death, termed apoptosis. The decision of a cell to live or die can be determined by the local environment of interleukins, protein factors that affect primary cells and are derived from immune cells. Interleukin 10 (IL-10) has been shown to have anti-apoptotic properties as well as inhibitory properties on the cytokine synthesis of various cell types. IL-10 has been shown to have anti-tumor effects through the up regulation of tissue inhibitors of metalloproteinase (TIMPs) slowing metastasis and yet tumor cells have been found to produce IL-10 as a possible defense mechanism to evade host defense. Vital to the understanding of causes of cancer is the interaction of the malignant cell with the host environment, including factors produced by the malignant cell as well those generated during the immune response. Utilizing a newly developed strain of NZB mice in which the IL-10 gene was knocked out (IL-10 KO), this grant seeks to identify the role of IL-10 in the malignancy of B cells. B-1 cells are a major subset of B cells found mainly in the peritoneum. 15 years after their discovery many questions remain. B-1 cells from wild type and IL-10 KO mice will be cultured and passaged back into recipient mice. The effects of IL-10 on malignancy and metastasis can then be observed. Cultured cells will be treated with proliferative and apoptotic agents to elucidate further the role of IL-10 in cancer related mechanisms. Antisense strategies will be used in vitro and in vivo to confirm the effects of IL-10 and the IL-10 knock out gene. Cytokine redundancy and overlapping functions can be examined with this strategy. Micro arrays, ribonuclease protection assays and RT/PCR will be used to observe gene activation following experimentally induced decreases in IL-10. This grant seeks to understand the activation of IL-10 transcription in malignant and normal cells and the downstream genetic events associated with IL-10 production.