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Tumor Immunity, Autoimmunity, and Immune Surveillance of Genetic Integrity



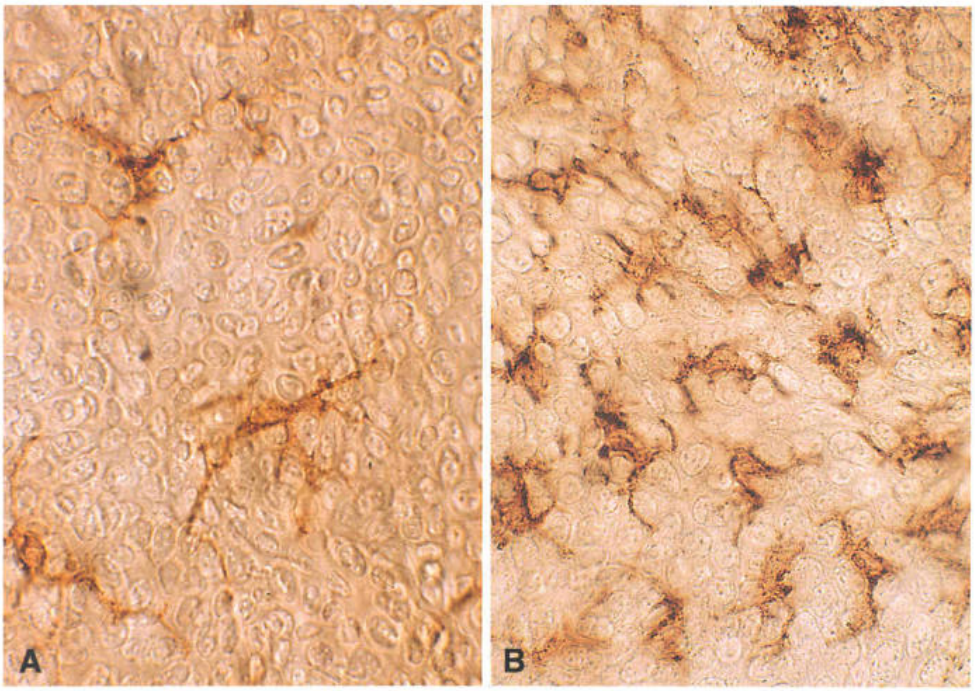
Mice immunized with DNA. The top mouse was immunized with control DNA, while the bottom mouse was immunized with DNA encoding a melanoma/melanocyte autoantigen tyrosinase-related protein 2. The bottom mouse developed autoimmunity manifested as depigmentation.

A primary focus of our laboratory is to better understand the host response to cancer. Our research has shown that the immune response to cancer is directed in large part toward self antigens also expressed by normal tissues. The finding that immune recognition of cancer is directed against self antigens raises the issue of how physiological mechanisms that maintain immune tolerance to self (to prevent autoimmunity) also form a barrier to cancer immunity. We have using melanoma models to investigate the similarities and differences between mechanisms for autoimmunity against normal tissues and tumor immunity (see Figure).

Strategies to break immune tolerance are being actively investigated in models of melanoma, breast cancer, prostate cancer, soft tissue sarcoma, and lymphoma, including: a) rational introduction of mutations into self proteins for active immunization; b) the application of cytokine adjuvants delivered as DNA to recruit and activate antigen-presenting cells (see Figure below) and to regulate T cells; c) modulation of the immune system using agonist monoclonal antibodies against the glucocorticoid-induced TNF receptor family protein (GITR) and other molecules expressed by lymphocytes; and d) the use of alkylating agent to induce homeostatic activation of immune cells and other host effects that promote cancer immunity and autoimmunity.

Another area of particular interest is how the adaptive immune system ignores or recognizes and responds to mutations. In this regard, we are investigating how the immune system reacts to different types of mutations in self proteins in healthy tissues of normal mice (to understand how the immune system might survey changes in genetic integrity) and in tumors. A goal is to understand adaptive immune recognition of mutations in incipient tumors and in tumors during progression (invasion into normal tissues and metastasis). The consequences of recognition of different types of mutations is investigated, including point mutations altering individual amino acids, premature stop codons creating truncated polypeptides, and nucleotide deletions producing altered reading frames. Immune recognition of alternative transcripts created through differential splicing or by cryptic translation start sites is also under investigation.

For these studies, we are using transgenic mouse models of cancer and transplantable tumor models to understand the roles of different immune and inflammatory cell populations in tumors and their draining lymph nodes. These models are used for at dissecting the roles for T cells, B cells, NK cells, NKT cells, and myeloid cells in promoting and/or preventing de novo tumors and their progression. In particular, we are applying intravital microscopy to follow the relationship of these different populations in three-dimensional space over time.



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