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IL-7R: A target in ALL and autoimmunity

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T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive hematological malignancy resulting from leukemic transformation of T-cell progenitors in the thymus. It accounts for approximately 15% of ALL cases in childhood and 20-25% in adults and is a leading cause of death in children. IL-7 and its receptor (IL-7R) play a critical role in normal T-cell development and homeostasis. Mutations in IL-7R were identified in 9% of pediatric T-ALL patients. These mutations usually involved insertions of three amino acids including cysteine and proline in the extracellular juxtamembrane region. WT or mutant forms of the human IL-7R (hIL-7R) from patients were retrovirally transfected into an IL-7-dependent murine thymic cell line D1. Mutant hIL-7Rs induced ligand-independent activation of the Jak-Stat and PI3K pathways, cell survival and proliferation. Notably, mutant hIL-7R-expressing D1 cells formed subcutaneous tumors in Rag1-/- mice, with substantial infiltration into various organs that are normally affected in advanced stages of T-ALL, such as bone marrow, liver, lymph nodes and spleen. Further functional assays revealed that mutant hIL-7Rs constitutive signaling required homodimerization via cysteines in the inserted sequences and downstream Jak1 activation and were IL-7, γc and Jak3-independent. Jak inhibitors were effective in blocking proliferation and survival of transformed cells. The hotspot for insertions lies in exon 6 in precisely the same region as a coding polymorphism regulating risk for MS and other autoimmune diseases, and we observe that this polymorphism affects strength of signaling. Our findings indicate that IL-7R mutations drive T-ALL, whereas polymorphisms that increase signaling promote autoimmunity, implicating IL-7R and Jak1 as therapeutic targets in these diseases.

Biography

Scott K Durum, Head of Immunological Cytokine Group, Laboratory of Molecular Immunoregulation and Deputy Laboratory Chief. After receiving his PhD in 1978, Dr. Durum received his postdoctoral training in immunology at the National Jewish Hospital in Denver and at Yale Medical School. Dr. Durum joined the Laboratory of Molecular Immunoregulation in 1984.

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Immunoregulation of E-FABP in breast cancer development

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Fatty acid binding proteins (FABPs) are known as central regulators of both metabolic and inflammatory pathways, but their role in tumor development remains largely unexplored. Here, it is reported that host expression of epidermal FABP (E-FABP) protects against mammary tumor growth. It was found that E-FABP is highly expressed in macrophages, particularly in a specific subset, promoting their antitumor activity. In the tumor stroma E-FABP-expressing tumor associated macrophages (TAMs) produce high levels of interferon β (IFNβ) through upregulation of lipid droplet (LD) formation in response to tumors. E-FABP-mediated IFNβ signaling can further enhance recruitment of tumoricidal effector cells, in particular NK cells, to the tumor stroma for antitumor activity. These findings identify E-FABP as a new protective factor to strengthen IFNβ responses against tumor growth.

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