ABSTRACTS
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7 At the interface of environment-immune interactions: cytokine and growth factor receptors. K.W. Kelley*, *University of Illinois, Urbana*.

Activation of the immune system by foreign environmental stimuli causes a number of important changes, including a reduction in feed intake and body growth. These effects are mediated by cytokine receptors that are expressed on a variety of cells. Insulin-like growth factor-I (IGF-I) is well known to promote lean body growth. The receptor for IGF-I is expressed on cells of the hematopoietic lineage. IGF-I not only increases mitotic activity of promyeloid cells, but it also acts as a survival factor (J. Immunol., 1999, 162:4542) and promotes differentiation into both neutrophils (J. Immunol., 2000, 164:113) and macrophages (Molec. Cell. Biol., 1999, 19:6229). The latter effects are mediated by the intrinsic tyrosine kinase activity of the beta chains of the IGF-I receptor, which leads to tyrosine phosphorylation of the insulin-receptor substrate-1 or -2 (IRS-1/2). Activated IRS-1/2 utilizes SH2 domains on the p85 regulatory subunit of phosphatidylinositol 3'-kinase (PI 3-kinase) to recruit the catalytic p110 subunit to the membrane. Cytokine and growth factor receptors are also expressed within the central nervous system. Recent evidence suggests that receptor signaling cascades for both tumor necrosis factor-α (TNF) and IGF-I routinely interact to affect cell survival (Proc. Natl. Acad. Sci. U.S.A., 1999, 96:9879). The ability of IGF-I to promote survival of cerebellar granule neurons is reduced by 50% with as little as 10 pg/ml of TNF. This is caused by the activated TNF receptor inhibiting the ability of IGF-I to tyrosine phosphorylate IRS-2 and to subsequently increase the enzymatic activity of PI 3-kinase. TNF has also been shown to inhibit protein synthesis in human skeletal myoblasts. We speculate that TNF acts similarly by silencing signals that emanate from the activated IGF-I receptor (Trends Neurosci., 2000, 23:175), thereby inducing receptor resistance. This hypothesis forms a molecular framework for understanding how co-activation of cytokine and growth factor receptors regulates animal growth and well being. (Supported by MH-51569, DK-49311 and AG-06246)

Key Words: IGF-I receptor, TNF receptors, Intracellular crosstalk