SESSION 6

Inflammation, Infection and Cancer Prevention

S18. Basic Mechanisms of Prevention of Inflammation-Induced Cancers

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Cytokine receptors exist in membrane bound and soluble form. While most soluble receptors are antagonists, some soluble receptors are agonists like soluble receptors of the gp130 cytokine family. In vivo, the IL-6/soluble IL-6R complex stimulates several types of target cells not stimulated by IL-6 alone, since they do not express the membrane bound IL-6R. This process has been named trans-signaling.

We have shown that the soluble gp130 protein, which is found in the circulation, is the natural inhibitor of IL-6/soluble IL-6R complex responses [1,2]. Soluble gp130 can be used as a molecular tool to discriminate between gp130 responses via membrane bound and soluble IL-6R responses [3–5]. We have constructed a fusion protein consisting of soluble gp130 and the Fc portion of human IgG1. This sgp130Fc protein proved to be highly efficient in blocking responses via the IL-6/soluble IL-6R complex without affecting IL-6 responses which are mediated via the membrane bound IL-6R [1–6].

The extent of IL-6 trans-signaling in chronic inflammatory diseases and cancer is controlled via the proteolytic release of the soluble IL-6R. The soluble IL-6R is released by metalloproteinases of the ADAM family, mainly by ADAM10 and ADAM17, and is tightly regulated by several stress parameters present in inflammatory states. These stress parameters include bacterial toxins, membrane damage and apoptosis. Using soluble gp130 protein we demonstrate that in several chronic inflammatory diseases and cancer including inflammatory bowel disease, peritonitis, rheumatoid arthritis and colon cancer, trans-signaling via the soluble IL-6R complexed to IL-6 is a crucial step for the development and the progression of the disease. Therefore, sgp130Fc is a novel therapeutic agent for the treatment of chronic inflammatory diseases and cancer [7,8].

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