Symposium B

Cytokine signaling and expression

SB-1

SIGNALING VIA RECEPTORS FOR PDGF AND TGF-β – POSSIBLE TARGETS FOR TUMOR THERAPY

CH Heldin

Ludwig Institute for Cancer Research, Uppsala University, Box 595, SE-751 24, Uppsala, Sweden (c-h.heldin@licr.uu.se)

Platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-beta) affect cell growth, survival and migration, and have important functions during the embryonal development. PDGF isoforms exert their cellular effects via two structurally similar tyrosine kinase receptors. Since PDGF promotes cell growth and survival, overactivity of the PDGF signaling pathway is associated with diesease, e.g. malignacies. We have explored the use of PDGF antagonists in tumor treatment, and found efficient inhibition of tumor growth in animal models of tumors driven by autocrine PDGF production. In addition, we have observed that inhibition of paracrine PDGF stimulation of stromal fibroblasts and vessel pericytes lowers tumor interstitial fluid pressure and tumor angiogenesis. TGF-beta has a more complicated role in cancer; initially TGF-beta is a tumor suppressor through its ability to inhibit growth and to promote apoptosis of tumor cells. At later stages, when tumor cells become insensitive to the cytostatic effects of TGF-beta, TGF-beta has tumor promoter effects through stimulation of epithelial-to-mesenchymal transition of tumor cells, stimulation of angiogenesis and suppression of the immune system. We are currently delineating the signaling pathways involved in the various cellular effects of TGF-beta, and exploring the possible use of TGF-beta antagonists in tumor treatment.

SB-2

VIRAL RECOGNITION AND TYPE 1 INTERFERON INDUCTION BY INNATE IMMUNE SYSTEM

Shizuo Akira

Research Institute for Microbial Diseases, Osaka University, and Exploratory Research for Advanced Technology (ERATO), Japan Science and Technology Agency, Suita, Osaka, Japan

Mammalian Toll-like receptors play a critical role in detection of invading pathogens as well as triggering of subsequent inflammatory and immune responses. Individual TLRs recognize different microbial components. The signaling pathways via TLRs are different each other, and the difference is in part due to selective usage of adaptor molecules. Besides TLRs, recent findings have shown the presence of cytosolic detector system of invading pathogens. Two DExD/H box RNA helicases, retinoic acid inducible protein-I (RIG-I) and melanoma differentiation-associated gene 5 (mda-5) are shown to be involved in anti-viral responses by recognizing dRNA in the cytoplasm. We recently identified a novel molecule named IPS-1that bridges between RIG-I/mda-5 and TBK-1, an essential molecule for IRF-3 phosphorylation and for subsequent type 1 interferon production. We have recently generated the mice lacking RIG-I, mda-5, and IPS-1, and in this symposium I will present data on the role of these individual molecule in viral infections.

SB-3

TRYPTASE-MEDIATED EXPRESSION OF CYTOKINES AND CHEMOKINES: CRITICAL ROLE OF IL-6 IN THE RECRUITMENT OF EOSINOPHILS AND NEUTROPHILS INTO THE CONJUNCTIVA BY MOUSE MAST CELL PROTEASE-7

Dai Miyazaki, Gilbert Jay, Chuan-Hui Kuo, Nobuhiko Nawata, Yoshitsugu Inoue, Richard L. Stevens, Santa J. Ono

Department of Ophthalmology, Tottori University, Tottori, Japan; Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and Department of Immunology, Institute of Ophthalmology, University College, University of London, London, England

Activation of mast cells (MCs) in patients with allergic conjunctivitis and mouse models of this FcεRI-dependent disorder lead to the release of undefined factors that ultimately leads to an accumulation of eosinophils and neutrophils in the inflamed tissue. We now report that mouse MC protease 7 (mMCP-7) is the most abundant MC-restricted protease in the conjunctiva of allergy-prone SWR/J mice. Recombinant mMCP-7 and its inactive zymogen were generated to evaluate the role of this MC-restricted tryptase in the eye. Injection of physiologic amounts of enzymatically active mMCP-7 into the conjunctiva of mMCP-7-expressing BALB/c mice and mMCP-7-null C57BL/6 mice resulted in increased numbers of eosinophils and neutrophils, but not lymphocytes. Because granulocyte accumulation did not occur in mice that received comparable amounts of pro-mMCP-7, mMCP-7 must be enzymatically active to exert its biological effects in the conjunctiva. Transcript profiling and bioinformatics data suggested that mMCP-7 activated an IL-6-dependent network. In agreement, mMCP-7 was unable to induce eosinophilia and neutrophilia in the conjunctiva of IL-6-null mice. The finding that IL-6 and mMCP-7 play key roles in the accumulation of granulocytes in the mouse's conjunctiva suggests their orthologs have comparable roles in patients with allergic conjunctivitis.