Symposium C

Gene regulation in host defense

SC-1

ACTIVATION AND INHIBITION OF CELLULAR INTERFERON RESPONSES AND INNATE ANTIVIRAL IMMUNITY

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Virus infection or stimulation virus replication intermediates like double-stranded RNA (dsRNA), initiate synthesis of interferon (IFN). The IFN signaling systems produce a broadly effective innate antiviral response that restricts the replication of diverse viruses. Most of the antiviral activity is the result of transcriptional programs initiated by virus infection, dsRNA, or IFN that activate antiviral gene expression. Treatment of mammalian cells with dsRNA can activate IRF3 and NFkB transcription factors to initiate IFN biosynthesis, and IFN signaling activates the ISGF3 transcription factor complex, composed of STAT1, STAT2, and IRF9. The importance of the IFN antiviral response is underscored by the numerous examples of animal viruses that have evolved strategies to destroy elements of this system. While they evolved to target antiviral responses, these virus systems provide unique insights into successful host targeting strategies that may have therapeutic value in control of cancer, inflammation, and other diseases characterized by hyperactive signal transduction.
One family of RNA viruses, the Paramyxoviruses, use their V proteins to engage in protein complexes that directly target STAT proteins and enable evasion of IFN-induced antiviral responses. Paramyxovirus V proteins can also inhibit IFN synthesis by disruption of signaling through the CARD-Helicase protein, MDA5. Investigation of MDA5 inhibition by V proteins has provided basic insights into specificity and selectivity determinants for negative regulation of innate dsRNA signaling. Examination of the endogenous dsRNA signaling inhibition by the helicase protein, LGP2, has also yielded mechanistic insights that suggest protein interactions are central to native feedback regulation of intracellular dsRNA signal transduction.

SC-2

THE ROLE OF INTERFERON-REGULATORY-FACTORS FOR TH1/TH2 CELL DIFFERENTIATION AS STUDIED DURING INFECTIONS

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Interferon-regulatory-factors comprise a family of 10 members defined by significant gene homology and by recognition of related DNA binding elements, originally known as the interferon-stimulated response elements (ISRE). The first members of the family were characterised by their potency to mediate effects of interferons intracellularly and, as a consequence, to contribute to the clearance of viral infections. Subsequently, it became clear that some family members are also decisive for appropriate Th cell differentiation. In this regard, IRF1, IRF2 and ICSBP (IRF8) are all non-redundantly required for an appropriate Th1 response, while IRF4 is decisive for Th2 cell differentiation. The effects of IRF4 are mediated within the Th cells themselves and seem to act mostly by interfering with the activity of GATA3, the master switch factor for Th2 cell differentiation. In contrast, IRF1 acts by regulating the expression of several different genes, which act in different cell types and are all stimulatory for a Th1 response. Therefore, IRF1 is probably the most important Th1 inducing transcription factor *in vivo*. As a consequence, deficiencies of IRF1 and IRF4 lead to profound disturbances in the immune reaction towards infections. In the talk, such immunodeficiencies will be exemplified by murine leishmaniasis and the infection with *Helicobacter pylori*.

SC-3

THE ROLE OF TUMOR NECROSIS FACTORS AND INTERFERONS IN HOST DEFENSE

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The members of the TNF/TNFR superfamily and interferons are critically involved in host defence against intracellular pathogens. The biological functions of these cytokines encompass beneficial and protective effects in inflammation and host defence as well as crucial roles in organogenesis. However, host damaging effects in sepsis and cachexia can also be mediated by this group of cytokines.
The lecture summarizes recent progress in the immunobiology of selected members of the TNF/TNFR superfamily and of signalling compents of the type II IFN receptor focusing on results obtained from animal studies using gene targeted mice.