TIm 02**ACTIVITIES OF TUMOR NECROSIS FACTOR.
D.N. Männel**

Tumor necrosis factor (TNF) is generated in sera of mice with activated reticuloendothelial system after injection of bacterial lipopolysaccharide (LPS) (E.A. Carswell et al., Proc. Natl. Acad. Sci. U.S.A. 72, 3666, 1975). Application of such sera to tumor-bearing mice induced hemorrhagic necrosis and complete regression of the tumors. This phenomenon resembled the LPS-induced tumor regression but lacked the toxic side effects of LPS treatment. Also, when assayed in vitro TNF is cytotoxic for tumor cells. We demonstrated that activated macrophages secrete TNF as one tumoricidal effector molecule (D.N. Männel et al., Infect. Immun. 33, 156, 1981). Studies with purified or recombinant TNF demonstrated specific receptors for TNF and the need for TNF internalization (F.C. Kull et al., Proc. Natl. Acad. Sci. U.S.A. 82, 5756, 1985). In contrast to the cytotoxic effect low concentrations of TNF induced protection against TNF cytotoxicity. Thus, TNF might have regulating properties on cellular metabolism. Molecular analysis of TNF revealed strong homology with another macrophage-derived mediator, cachectin (B. Beutler et al. Nature 316, 552, 1985). In vivo TNF like cachectin was lethal for mice. Polyclonal antibodies to TNF protected mice from the lethal effects of LPS (B. Beutler et al., Science 229, 869, 1985). Thus, TNF might play an important role in mediating the different metabolic effects induced by LPS.

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TIm 03**THERAPY WITH INTERFERON (IFN) ALPHA: CLINICAL TRIALS, INDICATIONS AND INTEGRATION IN THERAPEUTIC CONCEPTS.
F. Porzolt**

25 years after first description of IFN we learned to distinguish several subtypes and different receptors for IFN, we can measure proteins which are induced by IFN, we understand that immune functions are regulated by IFN, and we know that IFN can influence the expression and rearrangement of genes. This progress in understanding the biology of IFN is not yet followed by its therapeutic efficiency in cancer treatment. However, promising results have been obtained in myeloproliferative syndromes, Non-Hodgkin Lymphomas, multiple myeloma, and carcinoma of urinary bladder. It is accepted that Hairy Cell Leukemia (HCL) is the first established indication for treatment of a malignant disease with IFN alpha. Low daily s.c. doses of IFN alpha (0,5 Mio units) are effective; in the initial phase of treatment 2-3 doses/week are recommended; later 2-5 IFN applications/month may be sufficient. Using this regimen most side effects can be avoided. The efficiency of therapy is shown by fast clearance of HC from PB followed by an increase of platelets and subsequently by an increase of granulocytes and hemoglobin. Although complete remission of the disease are reported it remains to be established if HCL can be cured by IFN. Even if IFN is effective in a particular disease like HCL it has to be discussed if other effective therapies should be replaced by IFN-treatment. In HCL, splenectomy induces stable phases of the disease which are sustained for more than 10 years; therefore splenectomy should still be considered as primary treatment in HCL. Since so far only few patients can be treated efficiently by IFN it is important that these patients are included in basic research programs to find out when and why IFN is effective in cancer therapy. Tumorzentrum und Abt. Innere Medizin III, Universität Ulm, Steinhövelstr. 9, 7900 Ulm

TIm 04**DEFINITION OF DISCRETE SIGNALS MEDIATING HUMAN T CELL ACTIVATION VIA DIFFERENTIAL PATHWAYS : BIOLOGICAL AND CLINICAL RELEVANCE**

Stefan C. Meuer and Karl-Hermann Meyer zum Büschenfelde

Activation of the T cell systems represents a crucial requirement underlying specific immune responses. This process occurs as a well orchestrated series of events involving physical cell-cell interactions and secreted cell products i.e. lymphokines. Employing monoclonal antibodies reactive with receptor structures on the T cell surface in combination with pure sources of human lymphokines it has now become possible to identify two differential pathways through which human T lymphocytes can be activated to express their functional repertoires (antigen-receptor dependent pathway vs. "alternative" T11-mediated pathway). Moreover, discrete and stable intermediate stages of the activation cascade can be dissected which differ with regard to phenotype and function. Importantly, clinically observed immunodeficiencies can be attributed to blockades at one or another level of the activation process. Such studies point out new strategies of how to selectively manipulate impaired cellular immune responses in vivo.

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VBR 01**COMPARATIVE STUDIES ON CELLULAR ONCOGENES DURING NORMAL DEVELOPMENT AND TUMORIGENESIS**

M.Schartl, S.M. Robertson, F. Raulf, W. Mäueler, A. Barnekow¹

In order to contribute to an understanding of the normal function of cellular oncogenes, we are studying the expression of c-src, c-erbA, c-erbB, c-sis, c-fos, c-ras and c-myc during embryogenesis and in adult organs of vertebrates (incl. fish, frog, chicken and mouse) on the m-RNA-level. In the case of the c-src oncogene we are also studying the enzymatic activity of the protein gene product, which is a tyrosine specific kinase. The expression of the c-src gene was found to be organ-specific and age-dependent. During ontogenesis c-src expression is low during early embryogenesis (cleavage stages to late neurula stages), increases considerably during organogenesis and decreases thereafter to the level found in adult animals. Analysis of different organs revealed an organ-specificity with brain showing the highest kinase activities in embryos as well as in adults. Muscle shows high activities during organogenesis, but no or barely detectable activity in adult animals. For some of the other oncogenes investigated differential mRNA expression has also been observed, e.g. the c-sis oncogene shows high levels of expression in 7 day old neonates, and the c-ras gene shows different relative amounts of three m-RNA species during embryogenesis. We conclude from our data, that some oncogenes play a predominant role in differentiation rather than in proliferation processes during normal development. - In order to study the function of cellular oncogenes in tumorigenesis we have concentrated on the Xiphophorus melanoma system, where we have shown that both the cellular oncogene *lu* (encoding the genetic information for melanoma formation) and the c-src oncogene display a correlation in expression. For a functional analysis of this correlation we have cloned several alleles of the Xiphophorus src gene (*Xsrc*) and have started to clone *lu* by using a sib-selection strategy of clones from cosmid libraries in an in vivo assay. Max-Planck-Institut für Biochemie, D-8033 Martinsried and ¹ Inst. f. Med. Virol. d. Univ. D-6300 Giessen.