Session 10: Autoimmunity/Inflammation

Friday 16th April 2010. Moderators: Mark C. Glassy and Alois B. Lang

[10.45–11.15]

'Therapeutic antibodies in inflammatory/autoimmune diseases'

Alois B. Lang and Hervé Perron
Geneuro SA, Geneva, Switzerland

Chronic inflammation represents the key pathogenic event of many autoimmune diseases. Therefore it is not surprising that the majority of current and proposed treatment options are directed towards the modulation or suppression of the immune system. New approaches to the treatment of inflammatory and autoimmune diseases include the use of monoclonal antibodies (mAb) that block target pro inflammatory cytokines such as TNF α, various interleukins and complement, as well as cell surface receptors of B or T cells, or adhesion molecules. However, all therapeutic interventions that are capable of considerably altering the immune system carry the risk of significant short or long term adverse effects. Here we describe a novel therapeutic approach for the treatment of multiple sclerosis (MS) that is designed to act upstream of the inflammatory process, without targeting directly molecular or cellular components of the immune system itself. Our scientific strategy stems from our original discovery of viral particles specifically associated with tissues and cells collected from MS patients. The virus was named multiple sclerosis associated retrovirus (MSRV) to reflect its mode of replication and insertion into the host genome as unravelled by further molecular characterization studies. Indeed, further research led to the discovery of a previously unknown family of human endogenous retroviruses (HERVs) representing 8% of the human genome. MSRV is the founding member of HERW W, of a sub family of this large group of silent retroviral elements that under certain circumstances can encode full length viral proteins from specific loci. MSRV virions display superantigen like properties that are recapitulated by the envelope protein (MSRV Env); these include the activation of the innate immune system in a TLR4 dependent manner. Highly purified recombinant Env protein thus elicits pro inflammatory cytokine release by human peripheral blood mononuclear cells (PBMCs) in vitro, and acts as an adjuvant in the induction of experimental allergic encephalomyelitis (EAE) induced by myelin oligodendrocyte (MOG) protein in the mouse. Perhaps the most compelling argument in favour of an "immunological bias" induced by MSRV Env exposure in MS patients comes from the observation that PBMC from MS patients display a profile of cytokine production in response to stimulation by Env that is significantly different from that of PBMC from healthy donors. Most interestingly, there seems to be a significant correlation between the profile and amplitude of cytokine release by PBMC from MS patients, and the severity of the disease as assessed by the Expanded Disability Status Scale (EDSS). Our therapeutic approach is designed to block the inflammatory cascade initiated and/or potentiated by Env using mAbs that neutralize the Env protein thus preventing its TLR4 mediated effects on the immune system. We have developed several mAbs with the required properties. The lead compound, GNbAC1 binds the Env protein with high affinity and specificity. It has been proven to neutralize the biological effects of the Env protein both in vitro on cytokine production by PBMC and in vivo, using EAE models in the mouse. The humanized antibody will be evaluated in human clinical trials. Thus, unexpected findings on endogenous retroviral elements appear to open a new avenue of research and treatment options for MS, and, more recently, in patients with Schizophrenia associated with a systemic inflammatory component.

[11.15–11.45]

'CD44 and RHAMM (CD168), non-identical twins, are engaged in support of cell migration, and used as therapeutic targets in cancer and autoimmune inflammation'

David Naor
The Hebrew University, Jerusalem, Israel

We have found that CD44 substantially involved in various pathological aspects of cancer and autoimmune inflammations. We showed that injection of anti-CD44 monoclonal antibodies (mAbs) or gene vaccination with CD44 cDNAs markedly reduced pathological manifestations in animal models of cancer and autoimmunity. Focusing on the mechanism of these effects, we and others have found that cell surface CD44 supports cell migration and transmits apoptotic signals to target cells. However, normal innocent cells ,engaged in physiological functions, also use CD44 for trafficking or as a receptor for delivery of apoptotic signals. As alternative splicing can theoretically generate over 800 different CD44 variants, we predicted that cells engaged in pathological activities may express CD44 variants that are different than those expressed on cells involved in normal functions. Indeed, we found that joint inflammatory cells of patients with rheumatoid arthritis (RA) express a CD44 variant (designated CD44vRA), not expressed on normal cells of the same patient (Nedvetzki et al., J Clin Invest 111:1211-1220,2003). We generated monoclonal antibodies (mAbs) against this CD44 RA-specific variant, that killed by apoptosis joint inflammatory cells of RA patients, but not peripheral blood leukocytes from the same patient. Moreover, they also reduced collagen – induced arthritis (CIA) in DBA-1 mice, showing their therapeutic feasibility. This findings are translated now to a more clinical-oriented research in attempt to determine the clinical potential of anti-CD44vRA mAbs. We further found, that when CD44 is genetically depleted in embryonic mice, receptor hyaluronic acid-mediated motility (RHAMM, CD168), replaces its activity in supporting cell migration and maintenance of CIA (PNAS 101:18081-18086,2004). Interestingly, we recently discovered that injection of soluble RHAMM into NOD mice with type 1 diabetes induces resistance to the disease. The prediction that RHAMM induces active tolerance, which mediates the resistance to type 1 diabetes is now under investigation.

[11.45–12.15]

'Discovery and characterization of anti-inflammatory protease inhibitors'

Andy Nixon
Dyax Corporation, Cambridge, Massachusetts, USA

Abstract not provided.