Curcumin: Towards molecularly targeted chemoprevention of cancer

Ulrich Pfeffer [a], Adriana Amaro [a], Beatrice Bachmeier [b],
Giovanna Angelini [a]

[a] Functional Genomics, IRCCS AOU San Martino – IST Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy
[b] Institute of Laboratory Medicine, Ludwig-Maximilians-University Munich, Munich, Germany

Abstract

Everybody is at risk for cancer yet environmental factors, lifestyle and diet as well as genetic factors influence the individual cancer risk. Targeted or personalized cancer prevention is based on the knowledge of the molecular characteristics of the tumor to be prevented, the molecular mechanisms of action of the compounds to be used and the genetic make-up of the person who opts for prevention medicine. Genetic factors are to a certain extent specific for cancer types or even subtypes as it has been shown for breast cancer. The growing knowledge of such genotype cancer risk associations will allow for the definition of personalized prevention strategies. Prevention in intermediate risk populations requires non-toxic, well tolerated and cheap compounds. The main activity of the polyphenol Curcumin is the inhibition of nuclear factor kappa B (NFkB) activation. NFkB is involved in many cancers where it acts through the generation of chronic inflammation that can be contrasted by the anti-inflammatory activity of Curcumin. Curcumin mediated inhibition of NFkB leads to the interruption of a pro-metastatic positive feedback loop where NFkB induces the expression of inflammatory cytokines which in turn promote NFkB activation and the transcription of NFkB regulated pro-metastatic factors such as COX2, SPARC, ALDH3A1 and EFEMP1. By interrupting this loop Curcumin significantly reduces the formation of metastases in murine breast and prostate cancer models. Clinical trials for primary prevention must rely on a risk based selection of participants and well characterized response markers. Targeted cancer prevention can be applied as primary prevention, after diagnosis in low risk situations where watchful waiting could be integrated by prevention drugs and after adjuvant therapy to contrast the remaining risk of relapse. Adequately targeted, cancer prevention approaches are expected to outperform the effects of current cancer therapy in terms of overall survival.

TCR gene therapy of leukemia

Shao-An Xue

University College London Medical School, London, UK

Abstract

Conventional cancer therapies are limited by their toxicity and lack of specificity. To achieve targeted immunotherapy of cancer, we have chosen Wilm's Tumour antigen (WT1) as a target as it is over-expressed in most leukemia and many solid cancers. Using sophisticated WT1-TCR retroviral constructs, we have performed in vivo engraftment studies with CD34+ leukemic progenitor cells. In our model, treatment with WT1-TCR engineered patiens' T cells had cleared patients own leukemic cells. As the analysis of bone marrow indicated that control group showed evident engraftment of human leukemia cells, while the WT1-TCR treated group had none detectable. These data have provided a solid basis for a phase I/II clinical trial, demonstrating that WT1-TCR engineering of patient's T cells offers a simple and efficient way of producing tumor specific T cells to cure human leukemia.

Peptide mimotopes of malondialdehyde-epitopes for clinical applications in cardiovascular disease

Shahzada Amir, Karsten Hartvigsen, Oswald Wagner, Sotirios Tsimikas, Joseph L. Witztum, Christoph J. Binder

Medical University of Vienna, Vienna, Austria

Abstract

Introduction: Autoantibodies specific for malondialdehyde modified LDL (MDA-LDL) represent potential biomarkers to predict cardiovascular risk. However, the generation of MDA-LDL results in the formation of many different epitopes with high variability. Because it is not known, which MDA epitope is biological important, the aim of this study was to identify and characterize peptide mimotopes of MDA-LDL that could be used as antigens to improve the reproducible detection of MDA-specific autoantibodies.

Methods and Results: Peptide phage display libraries were screened for phages binding to the MDA-LDL specific natural IgM antibody LR04. After biopanning two consensus sequences (P1 & P2) of binding phages were synthesized. P1 and P2 were specifically bound by LR04, as the binding of LR04 to coated peptides was fully competed by MDA-LDL but not native LDL. P1 and P2 were also bound by other MDA specific murine (EN1) and human (IK17) antibodies. Furthermore, the binding of LR04 to late apoptotic cells was completely inhibited by both peptides, identifying them as mimotopes of naturally occurring epitopes on dying cells. Immunization of C57BL/6 mice with P2 conjugated to BSA, but not BSA alone, resulted in the robust induction of IgG1 and IgM antibodies against MDA-LDL. Moreover, serum IgG of immunized mice specifically stained epitopes in atherosclerotic lesion of rabbits and humans. Finally, we measured anti-mimotope antibody titers in serum samples previously collected from healthy subjects (n=17) and from patients (n=140) with stable angina pectoris undergoing percutaneous coronary intervention (Tsimikas, 2004). In patients a significant positive correlation was observed between anti-MDA-LDL and anti-mimotope IgM (P1, r=0.8; P2, r=0.6; p<0.0001) and IgG (P1, r=0.4; P2, r=0.3; p<0.0001) antibodies. A similar correlation was also found in sera of healthy subjects with IgM (P1, r=0.6; P2, r=0.4; p<0.0004) and IgG (P1, r=0.7; P2, r=0.5; p<0.0001) antibodies.

Conclusions: Thus, we have identified specific mimotopes of MDA-LDL that serve as highly reproducible antigens to assess autoantibody titers in patients with cardiovascular disease. Future studies will reveal their usefulness for therapeutic vaccination approaches against atherosclerosis.

Approaches in rare diseases and pediatrics across international boundaries

Michael N Liebman, Sabrina Molinaro

Strategic Medicine, Inc and IPQ Analytics, LLC, Kennett Square, PA, USA

Abstract

Rare diseases are designated as affecting less than 200,000 individuals (US) and of the approximately 7000 designated rare diseases, the majority of these occur in pediatric patients, and across international boundaries. An example is pediatric ARDS (Acute Respiratory Distress Syndrome) that is not diagnosed until a previously healthy child presents in the pICU with severe symptoms and in which more children die each year than from cystic fibrosis and leukemia, combined. The Nathaniel Adamczyk Foundation (NAF) is focused on identifying risk factors and opportunities for prevention of this devastating disease. Both the diagnosis and patient management are challenged by having to deal with a syndrome in a critical care situation in a heterogeneous patient population. NAF has undertaken the development of an (inter) national tissue and data