

Session 2: Cancer – I

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[09.45–10.05]

Lipoptosis, tumor-specific cell death via lipid accumulation induced by human monoclonal IgM antibody SAM-6

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Abstract: A balanced lipid metabolism is crucial for all cells. Disturbance of this homeostasis by non-physiological intracellular accumulation of fatty acids can result in apoptosis. This was proven in animal studies and was correlated to some human diseases, like lipotoxic cardiomyopathy. Some metabolic mechanisms of lipo-apoptosis were described and some causes were discussed, but reagents, which directly induce lipo-apoptosis, have so far not been identified. The human monoclonal IgM antibody SAM-6 was isolated from a stomach cancer patient by using the conventional human hybridoma technology (trioma technique). The antibody is coded by the germ-line genes IgHV3-30.3*01 and IgLV3-1*01 and is a component of the innate immunity to cancer. The addition of SAM-6 to tumor cells leads to an increase in the intracellular accumulation of lipids, followed by tumor cell apoptosis, named lipoptosis. This is to our knowledge the first description of this specific form of lipo-apoptosis as an antibody-mediated mechanism of tumor-specific cell killing. We present here new data on the 140 kD membrane bound SAM-6 receptor and details on the intracellular mechanisms of this new form of tumor-cell killing.

[10.05–10.25]

New mechanistic classes of antibody therapeutic for the potential treatment of tumor progression and angiogenesis

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Antibodies have played breakthrough roles in the treatment of cancer. In particular, antibodies have been used to target cytotoxic effector functions and toxins to tumor cells. More recently, antibodies have been clinically tested that are designed to inhibit positive regulators of tumor angiogenesis. We have developed two new mechanistic classes of antibody that have potential utility in oncology. Both have been derived from a unique phage display-based human Fab library in combination with an automation platform that allows us to select and screen thousands of antibodies. Firstly, we have isolated potent inhibitors of two serine proteinases implicated in prostate cancer progression. These antibodies inhibit the catalytic activity of the enzyme targets with K_i values as low as 50 pM. They do not inhibit the activity of other serine proteinases tested. Thus, this phage display approach allows the identification of potent and selective enzyme inhibitors with a speed unmay small molecule library screening and medicinal chemistry. Secondly, we have used this approach to identify a potent antibody agonist of the human TIE-1 receptor protein tyrosine kinase. The expression of this receptor is elevated on the tumor vasculature, and is induced by angiogenic signals such as hypoxia. However, a natural agonist has not been described and its function has been unclear. We have demonstrated that activation of TIE-1 inhibits endothelial cell migration in vitro. Ongoing preclinical studies will evaluate the efficacy of this potentially new class of tumor angiogenesis inhibitor.

[10.25–10.45]

Three ways to kill cancer cells with human antibodies

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Medarex is developing human monoclonal antibodies and antibody conjugates for the treatment of cancer and other diseases. The cancer pipeline includes molecules that direct the destruction of tumor cells by a variety of different mechanisms. MDX-010 is a human antibody in Phase II clinical development that binds to CTLA-4, a negative signaling receptor on T cells. The drug acts by enhancing patient immune responses to cancer cells. MDX-060 is a human antibody, also in Phase II clinical development, that binds to CD30 on Hodgkin's lymphoma and ALCL cells. Preclinical data demonstrate that the antibody mediates ADCC and, on cross-linking, directly blocks cell growth. Preclinical and clinical data on both programs will be presented. It is also possible to use human antibody conjugates to direct cytotoxic payloads to tumor cells. Preclinical data on Medarex antibody conjugates will be presented.

[10.45–11.05]

Anti-tumor monoclonal antibody effects on human NK cells

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Abstract: Most research exploring the role of NK cells and CD16 in monoclonal antibody (mAb) therapy of cancer has focused on antibody dependent cellular cytotoxicity (ADCC) and signaling induced by cross-linking CD16 with anti-16 mAb or immune complexes. Little is known about the changes that occur in NK cell phenotype and function when they interact with mAb-coated tumor under more physiologic conditions. We used a system consisting of peripheral blood mononuclear cells (PBMCs) and either autologous Epstein Barr Virus-transformed lymphoblasts (EBV-LBs) or breast cancer cells to assess how chimeric or CDR-grafted human IgG1 mAbs (rituximab, trastuzumab and apolizumab) impact on NK cell phenotype and cytokine production. Rituximab and trastuzumab induced down regulation of CD16 and upregulation of CD64 and CD54 expression by NK cells when the appropriate target cells (EBV-LBs or breast cancer cells) were present. Apolizumab (anti-HLA-DR) induced the same phenotypic changes in the absence of target cells in subjects with high baseline expression of the target antigen. Rituximab and apolizumab also induced production of IFN γ by NK cells when EBV-LBs were present. In the clinic, apolizumab, but not rituximab, induced transient loss of CD56+, CD16+ lymphocytes from the circulation of most patients. These studies suggest the role of CD16 and NK cells in the therapeutic response to mAb is not only to mediate ADCC directly, but also to induce phenotypic changes and IFN γ production by the NK cells which could then lead to enhanced tumor cell destruction by other mechanisms.