Symposium F

Cytokines, chemokines and interferons in cancer

SF-1

CYTOKINES CONTROLLING TUMOR IMMUNITY NETWORKS

MJ Smyth[1], JB Swann[1], Y Hayakawa[1], RD Schreiber[2], P Sivakumar[3], P Hertzog[4], SL Nutt[5]

[1]Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; [2]Washington University Medical School, St Louis, MO, USA; [3]Zymogenetics Inc. Seattle, WA, USA; [4]Centre for Functional Genomics and Human Disease, Monash Institute of Medical Research, Monash University, Clayton, Victoria; [5]The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

Cytokines play an important role in linking innate and adaptive arms in either natural or activated immune responses to growing tumors. We already appreciate the importance of TRAIL, and IFN-γ as effector molecules, but several key molecules that regulate the innate and adaptive immunity remain to be extensively investigated, including: IFN-γ, produced by activated dendritic cells (DC) and stressed tissue cells that can prominently affect T cells and NK cells; and IL-21, produced by activated T lymphocytes that enhances the maturation and functions of NK cells, and T and B cell memory. We have been using *in vitro* and *in vivo* mouse systems to dissect the role of IFN-γ and IL-21 in immune surveillance against cancer initiation, growth and metastasis. We have utilised both IFNAR1- and IFNAR2-deficient mice, as well as an IFNAR1-blocking antibody to investigate the role of type-I IFNs in controlling immune responses to tumors. Studies on a C57BL/6 background have demonstrated that endogenous type-I IFN is critical for controlling NK cell-mediated anti-tumor responses in a number of experimental tumor models, including protection from carcinogen (MCA)-induced sarcomas, resistance to the NK cell-sensitive, class I low RMA-S tumors and cytokine immunotherapy of lung metastases. Antibody neutralisation and depletion experiments demonstrated that type-I IFN signalling was essential early in the NK cell-mediated anti-tumor immune response. Cytokine immunotherapy using IL-12, IL-18 or IL-21 was effective in the absence of endogenous type-I IFN, however the anti-metastatic activity of IL-2 was abrogated in IFNAR-deficient mice, primarily due to a defect in IL-2 induced lytic activity. Further experiments have revealed an important anti-tumor activity of IL-21 alone, or in combination with other therapeutic approaches, in particular suggesting an ability to terminally differentiate NK cells and promote enhanced T cell memory.

SF-2

THE PRO-MALIGNANCY CHEMOKINES CCL2 AND CCL5 IN BREAST CANCER: ROLES, REGULATION AND PROGNOSTIC IMPLICATIONS

E Azenshtein E[1], G Soria[1], N Yaal-Hahoshen[2], S Shina[1], L Leider-Trejo[3], L Rivo[2], I Barnea[1], K Haim[1], EL Shabtai[4], I Greenberg[2], I Keydar[1], A Ben-Baruch[1]

[1] Dept. Cell Research and Immunology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv; [2] Dept. Oncology; [3] Dept. Pathology; [4] Statistical Service, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Elevated expression levels and incidence of the chemokines CCL2 and CCL5 in breast cancer patients are associated with early relapse and advanced disease, e.g. by virtue of their ability to promote the presence of deleterious macrophages at breast tumor sites. Analyses performed in our laboratory indicate that both chemokines act directly on the tumor cells to promote their ability to exert pro-malignancy activities, and that an intensive cross talk exists between CCL2 and CCL5 in breast tumor cells, through Erk-, PI3K and Src-mediated mechanisms. In addition, our findings indicate that the constitutive expression of CCL2 and CCL5 by breast tumor cells is regulated at the level of degradation, and that protection from degradation as well regulation at the transcription level may account for the ability of exogenous stimuli to elevate the expression of the chemokines by the tumor cells. Analyses performed on the expression of CCL2 and CCL5 in biopsies of breast cancer patients suggest that the expression of the two chemokines is associated with breast cancer development, and that combined expression of both chemokines together in the same tumor may drive forward the progression of disease. Furthermore, our recent study performed on stage II breast cancer patients indicates that CCL5 is a significant predictor of disease progression in this group of patients, and that the expression of the chemokine strengths the prognostic value of a conventional marker used in the clinic, namely estrogen receptor α. Together, our studies shed light on the involvement of CCL2 and CCL5 in breast cancer at the molecular and clinically-relevant levels.

SF-3

VIRUS-INDUCED IFN-α/β PROMOTES ISOTYPE SWITCH OF NEUTRALIZING ANTIBODY RESPONSES

Bach P[1], Kamphuis E[1], Odermatt B[2], Buchholz JB[3], Kalinke U[1]

[1]Division of Immunology, Paul-Ehrlich-Institut, Langen, Germany; [2]Department of Pathology, University Hospital Zürich, Zürich, Switzerland; [3]Division of Medical Biotechnology, Paul-Ehrlich-Institut, Langen,Germany

Rapidly after vesicular stomatitis virus (VSV) infection, IFN-α/β is induced to confer initial survival, whereas long term protection is granted by neutralizing antibody responses. As soluble antigens such as chicken gamma globulin induce enhanced antibody responses if administered together with IFN-α/β, we addressed whether virus-induced IFN-α/β had also an impact on the induction of neutralizing antibody responses. Because IFN-α/β receptor deficient (IFNAR$^{-/-}$) mice succumb to infection with live VSV within days and UV inactivated VSV induces primarily IgM, we generated replication deficient retrovirus-like particles (VLP) displaying the glycoprotein of VSV (VLP-VSV). Reminiscent of live VSV, VLP-VSV induced VSV neutralizing IgM responses that switched to IgG in a T help dependent manner. Interestingly, IFNAR$^{-/-}$ mice immunized with VLP-VSV mounted neutralizing IgM but did not show the IgG switch. The absence of isotype switch was related with a reduced germinal centre reaction. Mice selectively lacking IFNAR on lymphocytes showed normal antibody responses against VLP-VSV and live VSV. Thus, virus-induced IFN-α/β is critically involved in promoting the T help-dependent switch from virus neutralizing IgM to IgG whereas it is not required for the induction of neutralzing IgM. In contrast to exogenously administered IFN-α/β, virus-induced IFN-α/β does not act directly on lymphocytes.