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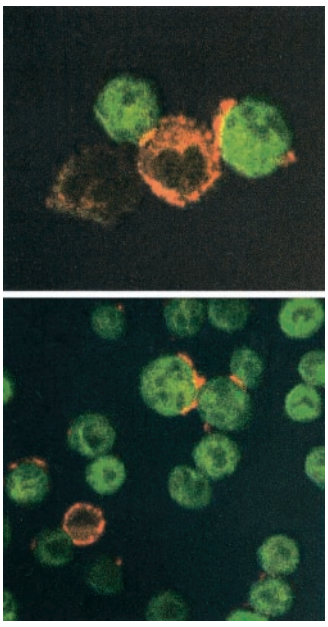
IN THIS ISSUE

Dual nectin receptors on NK cells



The NK activating receptor DNAX accessory molecule-1 (DNAM-1) recognizes the poliovirus receptor (PVR) that is expressed on some tumor cells. PVR is a member of a large family of Ig-like molecules called nectins and nectin-like proteins. The number of receptors for nectin family members is unknown. Fuchs et al. (p. 3994) discovered that a human NK cell line that did not express DNAM-1 bound the ectodomain of an IgG-PVR fusion protein. A mAb, raised by injecting mice with DNAM-1$^-$ NK cells, blocked the interaction of PVR with the DNAM-1$^-$ NK cells. The pattern of mAb reactivity with cells was similar to that seen for CD96 (Tactile, or T cell activated increase late expression) which is structurally similar to DNAM-1. Murine mastocytoma cells stably transfected with CD96 cDNA bound a fusion protein containing the entire PVR and one containing only a membrane distal Ig domain of PVR; anti-PVR and anti-DNAM-1 mAbs inhibited binding of both proteins. The transfected mastocytoma cells, but not untransfected cells, conjugated with T cells within 30 min at 0°C or 37°C. DNAM-1$^-$ NK cells conjugated with human B cells transfected with PVR acquired PVR and down-regulated CD96. Engagement of CD96 on human polyclonal NK cell lines by Ab activated NK cells and increased their lysis of mastocytoma cells. The authors conclude that the dual receptor system enables NK cells to adhere to and acquire tumor cell nectins and speculate that nectin acquisition renders NK cells targets for NK killing.

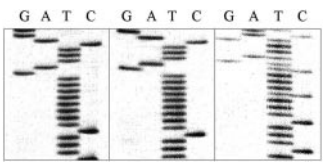
H-2M and MHC class II repertoire

The class II-associated peptide (CLIP) derived from the type II membrane glycoprotein, invariant chain (Ii), interacts with the peptide-binding groove of the MHC class II molecule to regulate MHC peptide loading. However, it is not clear how the affinity of CLIP for MHC class II affects the peptide repertoire. Honey et al. (p. 4142) developed strains of transgenic mice in which the mouse Ii was replaced by a wild-type human Ii (hIi^{WT}) gene or by an hIi gene with mutations in the CLIP region that decreased its affinity for I-A^b (hIi$^{BAD\text{-}CLIP}$). Cell surface expression of I-A^b and MHC class II was comparable in both transgenic strains. CLIP degradation products were more diverse in the hIi$^{BAD\text{-}CLIP}$ mice and readily dissociated from MHC class II molecules. Expression of MHC class II in H-2M$^{-/-}$ mice was rescued fully by crossing in hIi^{WT} but only partially by crossing in hIi$^{BAD\text{-}CLIP}$. Both MHC class II peptide loading equal to that of wild-type mice and efficient Ag presentation to T cells were seen with splenocytes from hIi^{WT} and hIi$^{BAD\text{-}CLIP}$ animals. But, the additional lack of H-2M in the two strains greatly increased the peptide loading and diversity of the repertoire and elicited a greater T cell response in those animals carrying hIi$^{BAD\text{-}CLIP}$ vs hIi^{WT}. Expression of hIi$^{BAD\text{-}CLIP}$ restored CD4$^+$ T cell levels in Ii$^{-/-}$H-2M$^{-/-}$ mice to 60% of those of wild-type mice, whereas hIi^{WT} had no affect on CD4$^+$ T cell levels. The authors propose that H-2M acts as a chaperone to stabilize the peptide:MHC class II complexes in the face of lowered CLIP affinity.

Rethinking glomerulonephritis

Linear binding of IgG to the glomerular basement membrane (GBM) is the hallmark of Goodpasture's syndrome. However, the precise mechanism by which autoantibodies are induced in glomerulonephritis (GN) has not been determined. Wu et al. (p. 4567) expanded studies on their rat model of GN in which transfer of T cells specific for the Goodpasture's Ag on collagen IV, Col4α3NC1, or injection of a T cell epitope, pCol (28–40), derived from the Ag could induce anti-GBM GN. GBM-bound IgG was detectable by immunofluorescence 5 days after glomerular injury in 76% of peptide-injected rats. Eluted GBM-bound IgG, but not circulating anti-pCol (28–40), immunostained native GBM in kidney sections; anti pCol (28–40) Ab, but not eluted GBM Ab, reacted with the peptide. A pCol (28–40) peptide with a substitution at aa 33 (p33A), within the T cell epitope, was unable to induce GN in injected rats. In contrast, a pCol (28–40) peptide with a substitution at aa 40 (p40A), that mutated a B cell epitope nested within the T cell epitope, and a derived 11-mer, pCol (29–39), did induce GN. Binding of IgG to GBM was detected in 65% of rats immunized with p40A but in no animals immunized with p33A. The immunofluorescent staining pattern of eluted anti-GBM Abs on GBM was broader than a control Col4α4-specific mAb; the eluted Ab immunoprecipitated only native GBM proteins. The authors conclude that a single T cell epitope of Goodpasture's Ag can initiate severe GN and leads to the subsequent production of anti-GBM Ab.

A novel IFN-γ-induced protein



Interferon-γ stimulates expression of a wide variety of genes in response to viral infection or inflammation. One of those genes is uteroglobin, the founding

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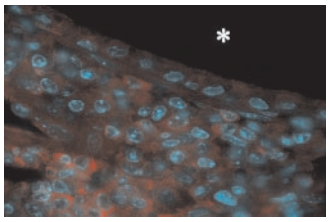
member of the newly formed secretoglobin (SCGB) superfamily of proteins. A new member of this family of proteins characterized by anti-inflammatory, anti-chemotactic tumor suppressor-like activities is described by Choi et al. (p. 4245). RT-PCR amplification of total RNA from a human lymphoblast cell line using primers for one member of the SCGB family, lipophilin-B, yielded a DNA sequence that was unrelated to lipophilin-B. The open reading frame of 252 nucleotides encoded a protein of 83 aa and was derived from a 3-kb gene on human chromosome 11. High level expression of the mRNA was detected in ovary, lymph node, tonsil, and a lymphoblast cell line. As the expression of this mRNA was induced in lymphoblast cells by IFN-γ, but not by other cytokines, the authors named it IIS (IFN-γ-inducible secretoglobin). IIS mRNA expression was stimulated in activated $CD8^+$ T cells and $CD19^+$ B cells compared with resting cells. Chemotactic migration and invasion of lymphoblast cells transfected with IIS antisense oligonucleotides were inhibited compared with untreated or IIS sense oligonuleotide-transfected cells. The authors speculate that this newest member of the SCGB superfamily may mediate IFN-γ-induced immunological functions.

Asthma and exercise

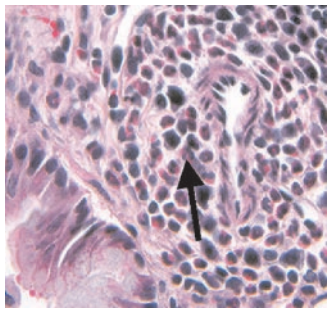


The American Thoracic Society guidelines for pulmonary rehabilitation programs recommend low to moderate intensity aerobic exercise for individuals suffering from chronic respiratory disease, including asthma. However, there is little information about the effect of exercise on asthmatic inflammatory responses. Pastva et al. (p. 4520) evaluated OVA-mediated changes in the lungs of OVA-sensitized mice. The lungs of sedentary mice receiving OVA i.p. on days 0 and 14, followed by aerosolized OVA on days 21–26, had increased inflammatory cellular infiltration, mucus production, epithelial hypertrophy, increased levels of chemokines KC and macrophage chemoattractant protein-1, and reduced expression of the adhesion molecule vascular cell adhesion molecule-1. In similarly treated mice that exercised 1 h on a motorized treadmill after aerosolization, those parameters were the same as in the control aerosolized but nonsensitized mice. Levels of IL-4 and IL-5 produced by Th2 cells were reduced ~13- and 3-fold, respectively, in bronchoalveolar lavage fluid from the lungs of sensitized, exercised animals vs sensitized, sedentary mice. Exercise decreased OVA-specific, but not total, IgE levels in sensitized animals, and decreased the phosphorylation of IκBα and translocation of the NF-κB subunit p65 in lung cells seen in sedentary mice. The authors conclude that moderate intensity aerobic exercise reduces asthmatic inflammation of the lung by modulating NF-κB activation.

IL-12-inducible genes

Although IL-12 is being used clinically to treat human cancers, the cellular and molecular mechanisms of the antitumor and antimetastatic activities of the cytokine are not fully understood. For example, many IL-12 effects are mediated through IFN-γ, yet IL-12 antitumor activity is seen in IFN-γ-deficient mice. Shi et al. (p. 4111) studied the genome-wide effects of IL-12 on growth and metastasis of a mouse mammary tumor cell line, 4T1, in syngeneic wild-type and IFN-$\gamma^{-/-}$ BALB/c mice. IL-12 was injected into the animals every 2 days beginning 7 days after s.c. injection of 4T1 cells. The IL-12-treated mice had tumor growth reduction (36% in wild-type and 31% in IFN-$\gamma^{-/-}$ mice) compared with untreated controls; both also had fewer lung metastases, with a greater effect seen in the treated wild-type animals. IL-12 blocked the formation of blood vessels and increased the number of tumor-infiltrating lymphocytes. Lung metastases were reduced in animals whose primary tumors were removed on days 14 and 21 and then given IL-12 compared with untreated animals. Tumor growth and metastases in naive mice were identical for tumors from untreated or IL-12-treated mice. Global gene expression analyses were performed on RNA samples from four groups of tumors on day 28: wild type and IFN-$\gamma^{-/-}$, each treated with either PBS or IL-12. Four distinct gene clusters were identified: 67 IFN-γ-independent and 50 IFN-γ-dependent genes had enhanced expression with IL-12, and 65 IFN-γ-dependent and 2 IFN-γ-independent genes had reduced expression with IL-12.

Collateral priming of T cells



Although atopic patients sensitized to one allergen frequently become sensitized to other environmental allergens, the relative roles of the innate and adaptive immune systems in this cross-sensitization have been unclear. Eisenbarth et al. (p. 4527) adoptively transferred Th2 cells expressing a transgenic TCR specific for an OVA peptide into naive mice. Transgenic Th2 cells were recruited into the lungs of the recipient mice after the first, but not after the second, OVA challenge by inhalation. However, there was an influx of eosinophils and a 3-fold increase of endogenous $CD4^+$ T cells in the lungs after a second OVA challenge. The inflammatory response to the second OVA challenge was not seen in $CD4^+$ T cell-deficient recipients of transgenic cells. No inflammatory response was seen if BSA was used for the second challenge. An inflammatory response and BSA-specific IgE were elicited by a secondary challenge with BSA only if both BSA and OVA, but not BSA alone, were present during the first challenge. Mice primed in vivo by i.p. injection of OVA followed by a first challenge with BSA and OVA together responded with lung eosinophilia and Th2 cytokine production during a second challenge with either BSA or OVA. The responses were not altered in mice deficient for Toll-like receptor 4 or MyD88. But, when the transferred transgenic TCR Th2 cells were IL-4 deficient, the BSA-specific Th2 secondary response was lost in both wild-type and IL-$4^{-/-}$ recipients. The authors use the term "collateral priming" to describe the IL-4-dependent and $CD4^+$ T cell-dependent activation of naive T cells to their cognate Ag by adaptive immune signals.

Summaries written by Dorothy L. Buchhagen, Ph.D.