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In This Issue

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PCSK9 works on the outside to bring down LDLR levels Individuals with a gain-of-function mutation in one of their genes encoding the serine protease proprotein convertase subtilisin/kexin type 9 (PCSK9) are hypercholesterolemic. Although known to be caused by PCSK9-mediated decrease in the number of LDL receptors (LDLRs) expressed by hepatocytes, the precise mechanisms by which PCSK9 engenders hypercholesterolemia have not been previously determined. Here, Lagace and colleagues show that exogenous PCSK9 decreases the number of LDLRs expressed at the cell surface of human hepatoma cells (pages 2995–3005). This decrease occurred when exogenous PCSK9 bound cell-surface LDLRs, initiating PCSK9 and LDLR internalization to the late endocytic compartment. Importantly, results of further studies using mice overexpressing PCSK9 indicated that PCSK9 secreted into the plasma decreased the cell-surface expression of LDLR by the hepatocytes of wild-type parabiotic partners. This decrease was concomitant with an increase in plasma LDL-cholesterol concentrations. These findings indicate that PCSK9 secreted into the plasma regulates the level of LDLR expression by hepatocytes. The authors suggest that blocking PCSK9 function in the plasma might provide a new approach for developing drugs to treat hypercholesterolemia.Type I IFNs beat IFN-γ to immunoproteasome induction in viral infections The MHC class I–bound peptides recognized by CD8+ T cells are generated by a protein complex known as the proteasome. The cytokine IFN-γ is known to […]

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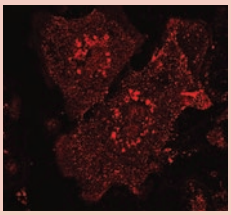
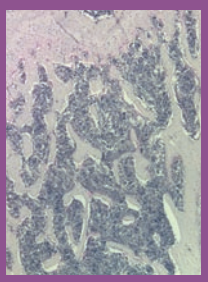


Type I IFNs beat IFN-γ to immunoproteasome induction in viral infections

The MHC class I–bound peptides recognized by $CD8^+$ T cells are generated by a protein complex known as the proteasome. The cytokine IFN-γ is known to alter the composition and function of the proteasome by inducing the transcription and translation of 3 alternative proteasome subunits. These replace their constitutively expressed counterparts to generate the immunoproteasome. As type I IFNs are expressed prior to IFN-γ following viral infection, Shin and colleagues investigated whether type I IFNs could induce the formation of the immunoproteasome (pages 3006–3014). Type I IFNs were found to induce the expression of the 3 immunoproteasome subunits in human hepatoma cells and primary hepatocytes as well as the assembly and proteolytic function of the immunoproteasome. Furthermore, transfection of human hepatoma cells with HCV RNA induced the expression of the 3 immunoproteasome subunits in an IFN-β–dependent manner. Importantly, expression of the immunoproteasome in the livers of chimpanzees infected with HCV occurred with the same kinetics as type I IFN expression and before the induction of IFN-γ. However, expression was transient and did not coincide with $CD8^+$ T cell infiltration. The authors therefore suggest that treatment with exogenous type I IFN, a highly effective therapy for acute HCV infection, might sustain immunoproteasome expression and increase the chances that virus-infected cells are recognized by liver-infiltrating $CD8^+$ T cells.

Double trouble for RA patients: PLCγ2 regulates osteoclastogenesis and B cell differentiation

In individuals with rheumatoid arthritis (RA), the autoimmune response not only attacks the joints, it also leads to the recruitment and/or differentiation of osteoclasts. Current treatments for patients with RA target either the joint-specific immune response or the osteoclast-mediated bone erosion. In this issue, Mao and colleagues report that phospholipase Cγ2 (PLCγ2), which was already known to regulate B cell differentiation, is required for normal osteoclast development and function in mice (pages 2869–2879). The authors show that trabecular bone made up a greater percentage of the total volume of the femurs of PLCγ2-deficient mice than wild-type mice. This increase in trabecular bone was accompanied by a decrease in the number of osteoclasts at the bone perimeter. Consistent with this decrease in osteoclasts, PLCγ2-deficient BM macrophages failed to differentiate into osteoclasts when stimulated with receptor activator of NF-κB ligand (RANKL). Further analysis indicated that PLCγ2 regulated osteclastogenesis through upregulation of nuclear factor of activated T cells c1 (NFATc1) and activation of activator protein–1 (AP1) and NF-κB. As PLCγ2 is already known to regulate the differentiation of B cells, one of the immune cells central to the pathology of RA, the authors suggest that targeting PLCγ2 might lead to control of both the immune-mediated joint destruction and the osteoclast-mediated bone erosion seen in RA.



Targting lung DCs in asthma

DCs are crucial activators of T cell responses, including the unwanted Th2 cell responses that occur in allergic asthma. Therapies that target DC function in the airways might represent a new way to treat individuals with allergic asthma. In this issue (pages 2935–2944), Idzko and colleagues show that inhalation of the immunosuppressive drug FTY270 — a sphingosine 1–phosphate receptor agonist currently in clinical trials as an immunosuppressive treatment for transplant recipients and for individuals with relapsing multiple sclerosis — suppressed the symptoms of allergic asthma in a mouse model of the disease. Inhalation of FTY270 both prior to and after initial allergen challenge suppressed the allergic Th2 cell response in the lungs and the generation of the Th2 cell response in the draining lymph node. This suppression occurred because FTY270 prevented lung DCs from migrating to the draining lymph node. Further in vitro analysis showed that DCs exposed to FTY270 were impaired in their ability to activate T cells. This demonstration that targeting lung DCs can suppress allergic asthma in mice might open new avenues of research for the development of drugs to treat individuals with allergic asthma.