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Macrophage SHP-1 deficiency in multiple sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) associated with considerable morbidity. Although several types of inflammatory cells are present within MS lesions, macrophages have gained increasing importance in the pathophysiology of the disease. SHP-1, a protein phosphatase that antagonizes innate and acquired immune cytokine signaling via NF- κ B, STAT1, and STAT6, has been implicated in activation of cytokine signaling in MS. Notably, in comparison with wild-type mice, SHP-1 knockout mice have a myelin deficiency that can be stimulated by Theiler's murine encephalomyelitis virus, resulting in rapid CNS inflammation, demyelination, and paralysis within one week of infection. These data have suggested that innate deficiency in SHP-1 may play a role in MS.

To explore the role of SHP-1 deficiency in MS, Christophi and colleagues isolated macrophages from MS patients and compared them with normal controls. They found that macrophages from MS patients were deficient in SHP-1 RNA and protein. Deficiency in SHP-1 was accompanied by increases in STAT6-, STAT1-, and NF- κ B-responsive genes. Thus, SHP-1 deficiency appears to play a role in the pathogenesis of MS through activation of inflammation in

macrophages. However, several important questions remain. Why is inflammation restricted to the CNS in these patients if there is a generalized macrophage SHP-1 deficiency? The authors suggest that viral infections in the CNS may interact with SHP-1-deficient macrophages. Another important issue is the mechanism of SHP-1 deficiency. Importantly, however, the authors of this paper have clearly identified macrophage SHP-1 deficiency as an important mediator of MS that is sure to provoke additional studies.

Cargo transport in eosinophils

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Eosinophils are among the most important cells in the immune system. They are involved in fighting off infections and are central to the pathogenesis of allergic airway diseases such as asthma and rhinitis. Pathologists recognize them histologically by their often bilobed nuclei and brightly eosinophilic granules on hematoxylin and eosin stain. Eosinophil granules are complex and contain a variety of proteins. Release of the contents of the granules is a critical component of eosinophil function. Methods of delivering granule contents include classical exocytosis, a process known as piecemeal degranulation (PMD) involving vesicular transport, and cytolysis. Different granule proteins can be selectively released by eosinophils by different methods.

Melo and co-workers set out to understand how eosinophil granule-derived major basic protein (MBP) makes

it way to the extracellular environment. This work is based largely on electron microscopic analysis using gold-labeled antibody fragments (immunogold). What emerges is the beautiful subcellular world that only electron microscopy can provide. The authors demonstrate that MBP is stored in secretory vesicles in addition to granules, and that it is transported to the extracellular world via PMD. This is important information that furthers our knowledge of the function of eosinophils. This amazing work also demonstrates the awesome power of electron microscopy and reminds us all that a good picture is irreplaceable, something that every pathologist can appreciate.

Credentialing a mouse emphysema model

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Mouse models have contributed greatly to the understanding of human disease. However, given the differences between mice and humans, great care is necessary in validating mouse models of human disease. Emphysema is a common lung disease that results in tremendous morbidity. Currently, there is no effective therapy. Therefore, mouse models

that recapitulate the salient features of emphysema would be helpful in delineating its pathogenesis and could be used as preclinical models to evaluate potential therapies. The pallid mouse contains a nonsense mutation at codon 69 of the pallid gene, which hinders the secretion of α_1 -antitrypsin into the circulation, consequently decreasing the inhibitory capacity of serum elastase, resulting in emphysema.

Although the pallid mouse was identified in 1931 and several studies have focused on its morphologic, biochemical, and genetic analysis, there has been little functional characterization of this important mouse model. Yoshida and colleagues have remedied this situation by fully credentialing the pallid mouse. They identified a wide array of deficiencies in both exercise capacity and respiratory function. Interestingly, the functional deficiencies preceded the morphological changes that have been described by several months, suggesting that functional deficits are more sensitive in the evaluation of emphysema in this model. This study illustrates the need for functional evaluation in mouse models, whenever possible, and provide an excellent framework for future studies using this important model.

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Cellular variability in response to death signals One of the fundamental questions facing biologists is how individual cells respond differently to the same biochemical stimuli. In a recent letter in *Nature*, Spencer and colleagues set out to understand why some cells in a clonal population survive and why some die after exposure to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). They examined individual cells via time-lapse microscopy to show that sister cells were more likely to die than randomly chosen cells after exposure to TRAIL. They found that the levels of several proteins involved in the premitochondrial outer-membrane polarization phase of apoptosis influenced the final decision to die. These results have implications in the use of TRAIL as an anticancer therapy and suggested to the authors that the efficiency of TRAIL-mediated cell killing could be increased by taking into account individual differences in response to TRAIL and designing strategies that involved drugging multiple targets. *Nature* 2009;459:428–432; doi:10.1038/nature08012

Master regulator of invasive behavior in cancer? In a recent article in *Nature Cell Biology*, Brandt and colleagues identified a novel protein they named suppressor of cancer cell invasion (SCAI). Gene expression studies indicate that SCAI downregulates β_1 -integrin. Furthermore, SCAI is frequently downregulated itself in a variety of cancers. Because β_1 -integrin is often overexpressed in cancer cells and is associated with more invasive and aggressive neoplasms, it is thought that loss of SCAI results in upregulation of β_1 -integrin in cancer cells. SCAI is also involved in expression of other genes and thus has the potential to control many facets of tumor cell invasion. However, many additional studies are necessary to identify the full spectrum of cellular activities influenced by SCAI. *Nature Cell Biology* 2009;11:557–568; doi:10.1038/ncb1862

How cancer cells gain access to the brain Until recently, the underlying mechanisms behind the ability of cancer cells to metastasize to specific anatomical sites had not been elucidated. As described in a recent letter in *Nature*, Bos and co-workers set out to explain how breast cancer cells metastasize to the brain. By selecting for breast cancer cells that preferentially metastasized to the brain, and using subsequent gene expression profiling, they were able to identify a set of genes that correlated with the ability to metastasize to the brain. Particular attention was paid to ST6GALNAC5, an α 2,6-sialyltransferase that is expressed specifically in brain. The authors hypothesize that cell-surface sialylation of breast cancer cells allows them to specifically penetrate the blood–brain barrier, facilitating brain metastasis. These findings suggest that ST6GALNAC5 may be a useful target in the prevention of brain metastasis in breast cancer. *Nature*, published online 6 May 2009; doi:10.1038/nature08021

Subversion of defense mechanisms

by pathogenic bacteria Pathogenic bacteria have numerous adaptations that allow them to exploit their hosts' defense systems. In a recent letter in *Nature*, Kim and colleagues discuss their discovery of a mechanism that allows pathogenic bacteria to overcome epithelial barrier integrity, one of the major host defense mechanisms. During infection, pathogenic bacteria deliver a variety of virulence factors, known as effectors, into epithelial cells. It turns out that one of these effectors, OspE, binds to integrin-linked kinase and stabilizes integrin-containing adhesion sites, which inhibits detachment of infected cells. Since infected cells do not detach, the pathogenic bacteria are able to maintain their infectious foothold. Interestingly, because OspE is strongly conserved in a number of pathogenic bacteria, targeting it could have general therapeutic relevance. *Nature* 2009;459:578–582; doi:10.1038/nature07952