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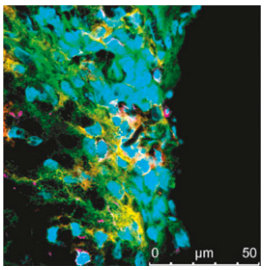
Driving DC Change



Both Th1 and Th17 cells are involved in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), and it has been found that Th17 cells can convert to the Th1 phenotype during the course of disease. Monocytes have also been implicated in EAE development and can colocalize with Th cells in the CNS. Davidson et al. (p. 1175) hypothesized that different subsets of activated murine Th cells could differentially affect the development of monocyte-derived dendritic cells (Mo-DCs) and, consequently, alter EAE pathogenesis. In vitro experiments demonstrated that activated Th1, Th2, and Th17 cells induced the differentiation of monocytes into Mo-DC subtypes, dubbed DC_{Th1}, DC_{Th2}, and DC_{Th17}, respectively. The DC_{Th17} subset produced large quantities of IL-12p70 following stimulation with a range of TLR ligands through a process that required CD40L and receptor activator of NF-kB ligand (RANKL), and these cells could promote the differentiation of naive T cells into Th1 cells in an Ag-specific manner. Interestingly, DC_{Th17} could also stimulate the reprogramming of Th17 cells into Th1 cells. In a Th17-driven model of EAE, T cells, monocytes, and DCs were observed to colocalize in the spinal cord, and $CD4^+$ T cells isolated from the spinal cord could induce the differentiation of monocytes into DCs. These DC_{ThEAE}, like the DC_{Th17}, produced IL-12p70 and promoted Th1 polarization. These data suggest a mechanism by which Th17 cell conversion into Th1 cells may occur during the course of autoimmune disease.

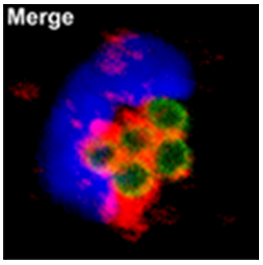
Enhancing γδ T cells with Zoledronate

Blocking the mevalonate pathway can be key to stopping malignant growth. The nitrogen-containing bisphosphonate (N-BP) zoledronate, used in a variety of cancer therapy regimens, achieves this through inhibiting farnesyl pyrophosphate (FPP) synthase. The ability of N-BPs to activate γδ T cells is of interest as these cells are often involved in immune surveillance and antitumor immunity. Zoledronate inhibition of FPP synthase causes an accumulation of the Vγ9Vδ2 T cell cognate Ag isopentenyl pyrophosphate, in turn driving γδ T cell activation, a process that is enhanced by IL-18. Nussbaumer et al. (p. 1346) demonstrated that while zoledronate inhibition of FPP caused an initial activation of γδ T cells, there was also downstream depletion of geranylgeranyl pyrophosphate (GGPP). As GGPP is a required molecule in protein prenylation, depletion resulted in cell stress, caspase-1–mediated maturation and release of IL-18 by human monocytes, and subsequent induction of the γδ T cell chemokine CCL2. Thus after an initial activation of γδ T cells, zoledronate toxicity inhibited γδ T cell expansion, an unwanted "brake" that could be reversed by the addition of GGPP. The authors determined that exogenous IL-18 eliminated the need for accessory cell costimulation and, with GGPP, enhanced the ability of zoledronate to generate effective γδ T cells. Thus, the authors provide important information on the mechanism of zoledronate action and how this therapeutic agent can be used, with dampened toxicity, to generate an ex vivo antitumor response from patient samples.

Co-complexing Complement

The complement pathway is critical to innate immunity and has three activation pathways (classical, alternative, and lectin) that converge at the C3 convertase. The lectin pathway functions similarly to the classical pathway but has a greater level of complexity, much of which remains to be characterized. Degn et al. (p. 1334) investigated the contributions of mannan-binding lectin (MBL)–associated serine proteases (MASP-1, -2, and -3) and the MBL-associated binding proteins [(MAp)19 and MAp44] to this complex activation process. Previous work determined that MASP-1 and MASP-2 are necessary for lectin pathway activation, with MASP-1 both transactivating MASP-2 and cleaving C2. MASP-2 cleaves both C2 and C4 to allow the formation of the C3 convertase. In this set of experiments, the authors demonstrated that whereas MASP-1 and MASP-2 do not form heterodimers in serum, they do form co-complexes together with MBL or ficolins. Ficolins are lectin-like molecules that are integral to the lectin pathway. The MASP co-complexes are necessary for activating complement and their serum concentration affects the extent of this activation. The authors proposed that MAp44, which has previously been shown to inhibit MASP-2 binding to MBL, disrupts these co-complexes that are essential for lectin pathway activation. Accordingly, the addition of MAp44 was able to block deposition of C4, a marker for complement activation. Taken together, the data provide a window into the mechanics of lectin pathway activation and show that MASP-1 and MASP-2 form activating co-complexes whose activity can be inhibited by the action of MAp44.

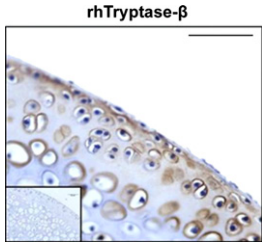
Steroids versus *Aspergillus fumigatus*



Immunocompromised individuals, including those who receive high-dose corticosteroids as part of chemotherapy regimens, are at higher risk for infection with the ubiquitous airborne mold, *Aspergillus fumigatus*. Patients with chronic granulomatous disease (CGD), who have genetic defects related to the NADPH oxidase, are also susceptible to invasive aspergillosis,

through a yet to be described mechanism. Kyrmizi et al. (p. 1287) have now elucidated this mechanism by investigating human monocytic cells infected with *A. fumigatus* spores. The authors found that the C-type lectin receptor Dectin-1 was ligated by fungal cell wall β-glucan, triggering a signaling cascade that resulted in recruitment of the autophagy protein LC3 II to the phagosome. The phagosomal recruitment of LC3 II was dependent on Syk kinase–mediated production of reactive oxygen species (ROS). Patients with CGD were unable to effectively recruit LC3 II to affected phagosomes. The autophagic pathway was important for fungal growth control, as short interfering RNA (siRNA) silencing of the autophagy gene Atg5 impaired the phagosome's ability to mature and eradicate *A. fumigatus*. In vivo and ex vivo corticosteroid administration stopped the recruitment of LC3 II to *A. fumigatus*–infected lysosomes by inhibiting ROS production. This was due to the corticosteroid inhibition of Src and Syk kinase phosphorylation. Thus, the authors conclude that defense against invasive aspergillosis requires phagosome maturation controlled by an autophagy-dependent mechanism that involves Syk kinase and ROS generation.

Tetrameric Tryptases Tackle Cartilage



Mast cell–derived tetramer-forming β-tryptases are abundantly produced in human synovium and can both support innate immunity and adversely affect the host during rheumatoid arthritis and osteoarthritis. In arthritic diseases, degradation of the proteoglycan aggrecan occurs through aggrecanolysis mediated by neutral proteinases, which Magarinos et al. (p. 1404) hypothesized could be activated by mast cell tetrameric tryptases. To address this possibility, they developed an ex vivo system to isolate the effects on cartilage of human (h)Tryptase-β and its ortholog, mouse mast cell protease-6 (mMCP-6). hTryptase-β caused aggrecanolysis in mouse femoral head explants but could not directly cleave aggrecan; however, the released aggrecan fragments contained neoepitopes consistent with proteolysis by a matrix metalloproteinase (MMP). In support of an MMP-mediated mechanism, explants treated with recombinant hTryptase-β or mMCP-6, or with lysates of mMCP-6–expressing but not mMCP-6–deficient mast cells, demonstrated increased MMP enzymatic activity and aggrecan loss relative to controls. Inhibitors of MMP-3 and MMP-13 significantly reduced mMCP-6–induced MMP activity and aggrecan release, and explants from mice with cartilage resistant to MMP cleavage showed hTryptase-β–induced MMP activation but were resistant to aggrecanolysis. Finally, hTryptase-β was shown to directly convert the inactive zymogen forms of human MMP-3 and MMP-13 into their enzymatically active forms in vitro. Targeting this mechanism of cartilage destruction via mast cell tetrameric tryptases may therefore find therapeutic utility in arthritic diseases.

More Autoantigen, Less Arthritis?

Macrophage scavenger receptor 1 (Msr1) binds modified self- and foreign-Ags and may be involved in maintaining peripheral tolerance. In this issue, Haasken et al. (p. 1055) investigated the effects of Msr1 on tolerance in the K/BxN TCR transgenic mouse model of spontaneous autoimmune arthritis. In these mice, $CD4^+$ T cells recognize the self-Ag glucose 6-phosphate isomerase (GPI) and provide help to GPI-specific B cells, which then produce anti-GPI autoantibodies that activate the innate immune system to cause joint damage. Both the incidence and severity of arthritis were reduced when *Msr1* was deleted in these mice (resulting in $Msr1^{-/-}$K/BxN mice). The initiation phase of disease, not the effector phase, was affected by *Msr1* deficiency, which reduced the production of anti-GPI autoantibodies compared with $Msr1^{+/+}$K/BxN mice. Although autoantibody production in this model requires T cell help, $Msr1^{-/-}$K/BxN mice had no apparent defects in T cell development or activity. B cells in these mice had a more naive phenotype than in $Msr1^{+/+}$K/BxN mice, but this reduced activation did not stem from a B cell–intrinsic defect. Msr1 activity was found to reduce the serum concentration of the self-Ag GPI, and normalization of GPI concentration by Msr1-expressing APCs restored arthritis to control levels. Suggesting a mechanism by which increased levels of serum autoantigen in $Msr1^{-/-}$K/BxN mice paradoxically resulted in decreased autoimmunity, these mice had fewer follicular helper T cells than controls, as well as evidence of reduced T:B cell interactions. Thus, the authors have identified a situation in which increased levels of autoantigen can reduce autoimmunity, further attesting to the complex nature of immunological tolerance.