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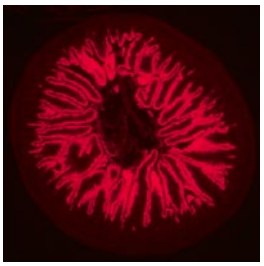
IN THIS ISSUE

RelA Protects the Gut



Although it has multiple proinflammatory activities, recent data suggest that NF-κB may play a protective role in colonic inflammation. Deletion of the NF-κB subunit RelA causes embryonic lethality, so Steinbrecher et al. (p. 2588) addressed the specific role of RelA in intestinal inflammation using conditional knockout mice lacking RelA in intestinal epithelial cells (IEC). Although ~10–15% of these IEC-RelA$^{-/-}$ mice showed severe gastrointestinal pathology and died before weaning, most displayed apparently normal intestinal development and survived to adulthood. An increase in the activity of the NF-κB subunit c-Rel was observed in IEC-RelA$^{-/-}$ mice, suggesting potentially compensatory actions by other NF-κB pathways. However, this shift in NF-κB activity did not fully compensate for RelA deletion, as IEC in IEC-RelA$^{-/-}$ mice demonstrated increased proliferation accompanied by increased apoptosis compared with wild-type controls. This dysregulation of apoptosis and proliferation was amplified in a model of dextran sodium sulfate-induced colitis, leading to increased mortality and a failure of appropriate intestinal restitution in IEC-RelA$^{-/-}$ mice. These data indicate an essential role for the RelA subunit of NF-κB in intestinal homeostasis and protection from mucosal injury.

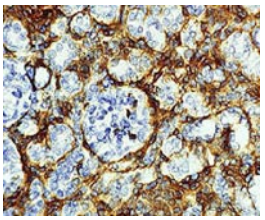
Flu Pathogenesis

Mouse and ferret models of influenza A virus infection do not accurately recapitulate the pathogenesis of infection in humans, and the contribution of the primate innate immune system to the control of influenza replication in vivo is not fully understood. Carroll et al. (p. 2385) set up a model of influenza A virus infection in rhesus macaques and analyzed the effects of oseltamivir (Tamiflu) on immune responses to the virus. As expected, treatment with oseltamivir effectively blocked viral replication and cytopathic effects in the trachea. Significant differences were not observed in the adaptive immune responses to influenza virus in oseltamivir-treated vs untreated animals, although there was a trend toward fewer influenza-specific T cells in treated animals. To examine innate immune responses, the authors measured the levels of mRNA for several antiviral molecules in tracheal secretions. Viral infection increased mRNA levels of IFN-α and of most IFN-inducible genes tested, but the expression of these genes did not differ significantly between oseltamivir-treated and untreated animals. In contrast, the levels of myxovirus-resistant protein (MxA) mRNA were significantly lower in untreated vs treated animals, suggesting that viral replication actively suppresses the expression of this important antiviral protein. This careful analysis of the effects of influenza therapy in primates advances our understanding of influenza virus pathogenesis.

Myasthenia Gravis Therapy

Current therapies for myasthenia gravis (MG) are not effective in all patients and are often accompanied by intolerable side effects. Mitoxantrone (MTX) is a potent antineoplastic drug that broadly affects the immune system and could thus be useful in MG treatment, but its use is limited by cardiotoxic side effects. The structurally related immunosuppressant Pixantrone (PIX) has reduced cardiotoxicity compared with MTX, so Ubiali et al. (p. 2696) examined the effects of PIX treatment on experimental autoimmune myasthenia gravis (EAMG), a rat model of MG. PIX treatment was shown to inhibit both mitogen-induced T cell proliferation and Ag-specific proliferation to immunodominant acetylcholine receptor (AChR) peptides in vitro and ex vivo. Next, the authors assessed the effects of PIX treatment in EAMG, either as a preventative or therapeutic treatment, and found that in both cases this drug ameliorated EAMG as measured by clinical score and reduction in body weight loss. Further analysis showed that PIX treatment restored muscle AChR content, reduced anti-AChR autoantibodies, and inhibited lymph node proliferative responses to AChR. PIX and MTX were found to be similarly effective in the treatment of EAMG, but the fewer toxic side effects of PIX indicate its promise for human MG therapy.

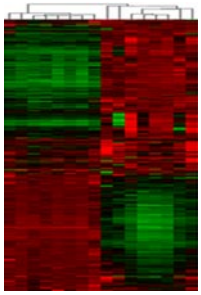
ITAMs and the Kidney



It has recently been discovered that ITAM-bearing receptors can transduce inhibitory as well as activating signals. One such receptor, FcαR1, promotes renal inflammation in multiple diseases via FcRγ and can also mediate both proinflammatory and antiinflammatory effects. Monovalent triggering of FcαR1 can inhibit inflammatory responses by coexpressed ITAM-bearing receptors, but it is not known whether it can affect non-ITAM signaling pathways. Kanamaru et al. (p. 2669) analyzed the effects of monovalent targeting by an anti-FcαR1 Ab (Fab A77) on inflammatory responses in myeloid cells and found that this Ab could inhibit the MCP-1 chemotactic response and TNF-α-induced cellular signaling. This inhibition was reversed by knockdown of the phosphatase SHP-1, indicating that SHP-1 is involved in the inhibitory ITAM (ITAMi) activities of FcαR1. Moving on to in vivo systems, the authors determined that Fab A77 treatment ameliorated inflammation in two different models of renal disease by reducing macrophage infiltration and fibrosis through a mechanism requiring the ITAM-containing FcRγ chain. These results were

extended to humans with the demonstration that Fab A77 inhibited TNF-α production by monocytes from both healthy volunteers and patients with renal disease via both autologous and heterologous receptor-activated responses. These data suggest that the induction of FcαR1 ITAMi signaling may provide a new approach to the treatment of inflammatory renal disease.

Cellular Signatures



Different cell types within an individual carry the same genome yet have distinct phenotypes. Stable epigenetic modification is presumed to account for these differences, but the discovery of histone demethylases has called into question the long-term stability of histone methylation. Miao et al. (p. 2264) sought to address this issue by analyzing the genome-wide dimethylation pattern of histone H3 lysine-9 (H3K9Me2) in different immune cells. H3K9Me2 modifications are predicted to repress transcription and fine tune cellular responses within a network of epigenetic modifications. Using chromatin immunoprecipitation coupled to DNA microarray analysis (ChIP-chip), the authors assessed the H3K9Me2 profile in lymphocytes and monocytes from healthy volunteers. Distinct patterns of H3K9Me2 were observed in lymphocytes vs monocytes, and these patterns were similar in all individuals studied irrespective of age or gender. Further analysis determined that H3K9Me2 was common in gene coding regions, promoters, and CpG islands and was enriched in monocyte- and lymphocyte-specific pathways. Another such modification, H3K4Me2, was also found to be distributed in a cell type-specific and stable manner across individuals of different ages and genders. These data suggest that histone methylation patterns are important to maintain cellular identity and could be used as diagnostic databases for human disease.

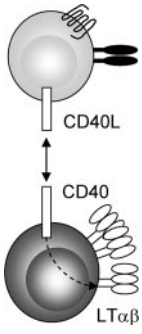
Driving Macrophage Activation

Classically activated macrophages mediate inflammation while alternatively activated macrophages promote inflammatory resolution, but the mechanisms responsible for these phenotypes are not fully understood. MacKinnon et al. (p. 2650) analyzed the roles of galectin-3 and its receptor CD98 in macrophages and found that these molecules were specifically involved in alternative activation. In vitro, galectin-3-deficient macrophages responded to classical stimulation similar to wild-type macrophages but were significantly less able to undergo IL-4- or IL-13-driven alternative activation. Accordingly, alveolar macrophages from galectin-3$^{-/-}$ mice showed a reduction in alternative activation markers compared with wild-type cells. These data were further supported by the observation that galectin-3 was down-regulated upon classical activation of macrophages but up-regulated upon alternative activation. Specific inhibitors of galectin-3 or CD98, or siRNA-mediated inhibition of either molecule, blocked IL-4-induced macrophage activation but did not affect classical activation. Further studies indicated that galectin-3 binding to CD98 activated the PI3K pathway, which drove alternative macrophage activation with some involvement of STAT6. Taken together, these data identify an important pathway required for alternative macrophage activation.

Rethinking HMGB1

High mobility group box protein 1 (HMGB1) is generally thought of as a proinflammatory cytokine that acts as a late mediator of sepsis; however, recent data have called this role into question. Using a defined in vitro system, Sha et al. (p. 2531) found that HMGB1 has no intrinsic proinflammatory properties but instead promotes inflammation only when bound to proinflammatory mediators such as IL-1β. HMGB1 was isolated from cells cultured in the presence or absence of the proinflammatory cytokines IL-1β, IFN-γ, or TNF-α and was then used to stimulate macrophages and neutrophils. HMGB1 purified from cells cultured without cytokines demonstrated no significant proinflammatory capabilities; however, HMGB1 purified from cells exposed to cytokines, particularly IL-1β, greatly increased the production of inflammatory mediators by macrophages. Western blotting demonstrated that IL-1β directly associated with HMGB1 in IL-1β-supplemented cultures. Further in vitro analysis showed that the HMGB1:IL-1β complex, but neither component alone, could induce macrophage and neutrophil cytokine production, and the proinflammatory effects of this complex were abolished in the presence of anti-IL-1β Abs or antagonists of the IL-1R. These data should help resolve the controversy regarding the abilities of HMGB1 to modulate inflammation.

Portrait of a Germinal Center



Successful germinal center (GC) reactions require complex cooperation between B cells, T cells, and follicular dendritic cells. ICOS and lymphotoxin (LT) have been identified as important participants in the GC reaction, but their relative roles have not been fully elucidated. To assess how ICOS mediates the initiation of a GC reaction, Vu et al. (p. 2284) analyzed GC reactions in ICOS$^{-/-}$ mice. As expected, mice lacking either ICOS or LTβ demonstrated defective GC formation and a reduction in differentiated GC B cells compared with wild-type. No differences were seen in LT$\alpha\beta$ expression in activated ICOS$^{-/-}$ vs wild-type lymphocytes or follicular B cells. However, ICOS$^{-/-}$ mice had a significant reduction in LT$\alpha\beta$ expression on GC B cells. In support of this observation, in vitro experiments demonstrated that ICOS signaling in T cells induced LT$\alpha\beta$ expression on B cells. Restoration of LT pathway signaling with an anti-LTβR Ab did not rescue the GC reaction, indicating that additional factors were involved in the GC defects in these mice. Restoration of GC T cell help by administration of anti-CD40 in ICOS$^{-/-}$ mice restored GC structures and induced LT$\alpha\beta$ up-regulation on GC B cells. This GC restoration was blocked by an inhibitor of the LT pathway. Thus, the proper development of a GC reaction requires ICOS-induced up-regulation of LT$\alpha\beta$ as well as cooperation between the LT and CD40 signaling pathways.

Summaries written by Jennifer Hartt Meyers, Ph.D.