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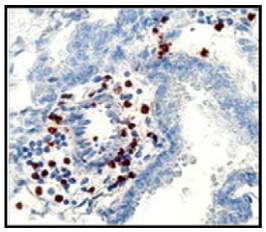
Remodeling with ORMDL3

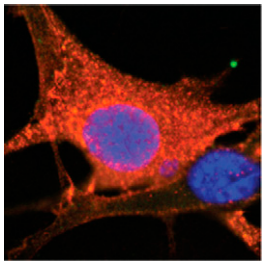


Orosomucoid-like 3 (ORMDL3), an endoplasmic reticulum (ER) transmembrane protein, has been linked to asthma in genome-wide association studies and in wild-type mice functions as an allergen whose expression can be induced by Th2 cytokines. Although previous in vitro studies showed that ORMDL3 activated ATF6, a transcription factor in the ER unfolded protein response pathway, the in vivo pathways regulated by this protein have yet to be determined. To address this, Miller et al. (p. 3475) generated a conditional transgenic mouse that expresses hORMDL3 in all cells when crossed to zona pellucida 3 Cre mice (hORMDL3$^{zp3\text{-}Cre}$). Evidence of asthma-associated airway remodeling, such as increased lung collagen, mucus, and peribronchial fibrosis, was observed in hORMDL3$^{zp3\text{-}Cre}$ mice starting at 4 wk of age. hORMDL3$^{zp3\text{-}Cre}$ mice, but not wild-type mice, exhibited increased lung expression of TGF-β1, ADAM8, CXCL10, and CXCL11, along with selective activation of ATF6. Increased lung levels of inflammatory IL-13 and IL-5, along with infiltration of peribronchial CD4$^+$ T cells, F4/80$^+$ macrophages, eosinophils, and neutrophils began at 8 wk of age, suggesting that airway remodeling preceded airway inflammation. Together, these data suggest a regulatory pathway by which an ER-localized protein promotes airway remodeling and the pathogenesis of asthma.

Seq-ing Diversity in HIV Antibodies

Rhesus macaque is often used as a nonhuman primate model of human humoral immunity in preclinical vaccine studies, spurring the recent detailed description of macaque germline Ig loci and the founding of a germline gene segment database to allow detailed analyses of Ab responses to vaccines. Sundling et al. (p. 3637) took advantage of these resources to investigate IgH gene segment usage in the B cell repertoire of both unvaccinated and recombinant HIV-1 envelope glycoprotein (Env)–vaccinated macaques. Using 454-pyrosequencing and single cell RT-PCR for the major Ig H chain V region gene families (IGHV 1, 3, and 4), the authors examined H chain V(D)J gene segment usage in total IgG-switched B cells from macaques and found that both techniques indicated broad usage of V-gene segments. The pattern of usage in macaques closely resembled that found in humans–42 of the 53 annotated macaque V-gene segments contributed to the circulating IgG-switched B cell repertoire; however, there was preferred usage of some gene segments over others. A comparison of total and Env-specific memory B cells in vaccinated macaques revealed that V-gene usage was highly diverse and similar in each group, although VH5.46 was used far more frequently in the Env-specific memory B cell pool. A calculation of the number of participating clonal lineages indicated that 502 of 606 functional sequences represented unique clonotypes, highlighting how administration of a vaccine based on a single protein Ag can elicit a B cell response comprised of highly diverse Ab specificities. Together, these results reveal a remarkable level of genetic diversity in B cells responding to Env vaccination and indicate that broad V-gene segment usage is integral to the breadth of Ab specificities found in this polyclonal Ab response.

Stressing about Viruses



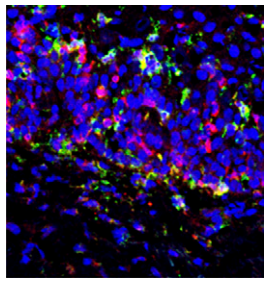
NF90, which has dsRNA-binding properties, is involved in host antiviral immune responses. NF90 interacts directly with RNA-dependent protein kinase (PKR), which regulates the formation of stress granules composed of RNA-binding proteins, a hallmark of the cellular response against viral infections. To further elucidate this mechanism, Wen et al. (p. 3753) first identified the C terminus of NF90 as the domain able to directly interact with PKR in mammalian cells. Using NF90 knockdown cells or mutant or truncated NF90-transfected cells, in the presence of either dsRNA (polyinosinic-polycytidylic acid [poly(I:C)]) or viral RNA, the authors showed that NF90 has a dual function in that it supports PKR phosphorylation at low NF90 levels, but inhibits PKR phosphorylation at high NF90 levels. NF90 was found to colocalize with stress granule markers in poly (I:C)-stimulated cells and the number of stress granules was significantly diminished in NF90 knockdown cells. Poly(I:C) activates PKR, and treatment with a PKR inhibitor reduced stress granule formation, demonstrating that NF90 regulation of this process is dependent on PKR. Expression of mutant NF90 indicated that both RNA binding and phosphorylation of NF90 are required for stress granule induction. Furthermore, infection of NF90 knockdown cells with an H1N1 virus strain led to significant viral replication. Dissection of this pathway with mutant viral strains that possessed attenuated PKR or IFN indicated that the antiviral response of the NF90–PKR pathway is independent of IFN-β. In this study, the authors identify a host antiviral mechanism involving NF90-mediated regulation of PKR activity and stress granule formation.

Reprogramming B Cells

Metabolism has a significant impact on lymphocyte homeostasis and immune responses; however, the role metabolism plays in B cell activation and Ab production is not well defined. To examine the involvement of

B cell metabolism in anergy and autoimmunity, Caro-Maldonado et al. (p. 3626) examined B cell metabolic reprogramming upon activation with LPS and demonstrated an increase in B cell glucose oxidation and an increase in both glycolytic and mitochondrial metabolic activity. Ag stimulation of B and T cells indicated that, unlike the activation-induced shift to a predominantly glycolytic metabolism in T cells, B cells increased both oxygen consumption rate and extracellular acidification rate, maintaining a balanced ratio between the two. B cell activation also led to increased mitochondrial mass and glucose uptake through the glucose transporter, Glut1. The authors demonstrated that anergic B cells are metabolically suppressed; as compared with control B cells, anergic B cells did not increase extracellular acidification rate and oxygen consumption rate in response to self-Ag, with only a minimal increase when further stimulated with LPS. Alternatively, B cells from BAFF transgenic mice, which are chronically stimulated via BAFF, had increased glycolytic rates and glucose metabolism upon LPS stimulation compared with control B cells. Inhibition of glucose metabolism significantly impaired B cell proliferation and Ab production, indicating the dependence of B cell function on glucose metabolism. Further examining B cell dependence on glycolysis, the authors found that transgenic mice with a B cell-specific deletion of Glut1 had reduced peripheral B cell numbers and deficiencies in Ab production. Understanding the metabolic reprogramming mechanisms behind B cell activation and Ab production and the impact of tolerance on these mechanisms may provide insight into B cell tolerance in autoimmune diseases.

Shedding Light on Cervical HIV



The female genital tract can act as a viral entry point and reservoir for HIV; however, extensive studies of the composition of immune cells and HIV viral load in the cervical tissue and how these factors correlate to plasma and cervical viral shedding have not been conducted. To address this issue, Gibbs et al. (p. 3947) collected and analyzed ectocervical tissues and genital secretions from HIV-seropositive (HIV^+) and HIV-seronegative (HIV^-) female Kenyan sex workers (FSW) and HIV^- lower risk (LR) women. Using in situ staining and quantitative imaging analysis, the authors determined that HIV^+FSW exhibited increased percentages of $CD8^+$ $CD3^+$ and HLA-DR^+ cells in the epithelium of ectocervical tissue compared with HIV^-FSW or HIV^-LR controls. An increased percentage of $CD8^+$ cells, but not higher HIV RNA expression or the presence of HLA-DR^+ cells (perhaps APCs), in ectocervical tissue correlated with higher HIV viral load in plasma and cervicovaginal secretion samples. HIV expression levels in plasma also significantly correlated with HIV expression in cervicovaginal secretion samples. These results provide insight into the relationships between local immune cell populations, cervical tissue HIV titers, and systemic viral HIV load in HIV^+ women and indicate a correlation between increased ectocervical $CD8^+$ T cells and heightened local and systemic viral shedding.