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Top Reads

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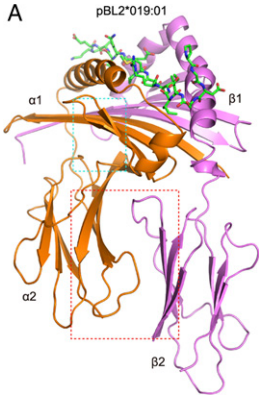
Lessons Learned from Chicken pMHC-II Crystal Structure

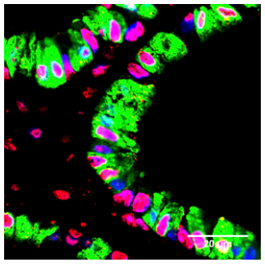


Despite playing a critical role in cellular and humoral immunity, there is very little structural information for peptide–MHC class II (pMHC-II) complexes in nonmammals. In this Top Read, Zhang et al. (p. 1630) report the crystal structure of a chicken pMHC-II complex (pBL2*019:01) and investigate the mechanism by which one monomorphic α-chain combines with two polymorphic β-chains to form a functional heterodimer. The crystal structure revealed an increase in hydrogen bonding between the α and β main chains at the central interface that derives from an insertion of four residues in the chicken α-chain. Analysis of the interactions between the α11 and α2 helices revealed no direct interaction; rather, the two helices connect indirectly through a molecule of water and P10-Ser. Additionally, the peptide-binding groove of pBL2*019:01 is more open at both ends than in other structures and interacts with the DM molecule mainly via contact with the α1 domain of pMHC-II close to the P1 pocket. Furthermore, because the chicken CD4 molecule carries a five-residue deletion, interaction between pBL2*019:01 and CD4 may be different. Thus, this study provides a new understanding of the pairing mechanism for α- and β-chains in a pMHC-II complex and establishes a structural principle to design epitope-related vaccines for the prevention of chicken diseases.

Core-2 *O*-Glycosylation Reports Notch Signaling in T Cells

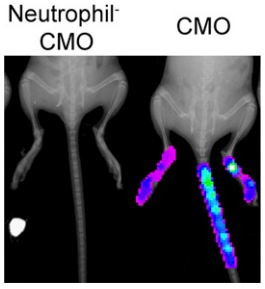
In this Top Read, Perkey et al. (p. 1674) demonstrate that core-2 *O*-glycosylation is a sensitive indicator of Notch signaling in activated T cells. Newly activated T cells upregulated expression of the *Gcnt1* glycosyltransferase gene, driving the switch from core-1 to core-2 *O*-glycosylation of CD43, which was distinguished using glycoform-specific mAbs. Core-2 *O*-glycosylation of CD43 correlated with Notch signaling in multiple models, including allotransplantation, immunization, and infection. Blockade of Delta-like ligands 1 and 4 decreased core-2 *O*-glycosylation of CD43 in a dose-dependent manner, suggesting that core-2 *O*-glycosylation is indicative of Notch signaling. Increased core-2 *O*-glycosylation correlated with Notch signaling in both $CD4^+$ and $CD8^+$ T cells. Core-2 *O*-glycosylation of CD43, however, was not necessary for disease progression. Using this new indicator of Notch signaling, the authors were able to show that fibroblastic stromal cells are a critical source of Notch signaling in graft-versus-host disease progression. These data provide a valuable method to use the glycosylation state of CD43 as a metric for Notch signaling in T cells.

cGAS Is Critical for the Induction of Allergic Asthma



Recent studies indicate that the DNA damage response can induce inflammation. As DNA damage has been observed in the bronchial epithelium of asthmatic mice, Han et al. (p. 1437) explored the role of the cyclic GMP-AMP synthase (cGAS) pathway, the major sensor of cytosolic dsDNA, in the pathogenesis of asthma. Asthmatic mice displayed an accumulation of cytosolic dsDNA in airway epithelial cells (ECs). Deletion of cGAS in airway ECs significantly attenuated allergen-induced inflammation as evidenced by a reduction in both total cell and eosinophil counts in the bronchoalveolar lavage fluid, as well as reduced IL-4, IL-5, and IL-13 mRNA and protein in lung homogenates. Additionally, deletion of cGAS in airway ECs attenuated production of IL-25, IL-33, and GM-CSF. Increased accumulation of cytosolic dsDNA was also observed in airway ECs of allergen-challenged mice treated with IL-33. Deletion of cGAS in these mice significantly decreased airway inflammation, including GM-CSF production, induced by allergen challenge. Pretreatment of IL-33–stimulated human bronchial ECs with a scavenger specific for mitochondrial reactive oxygen species reduced the accumulation of cytosolic dsDNA in these cells, likely by suppressing the release of mitochondrial DNA into the cytosol. Thus, airway EC cGAS plays an important role in sensing dsDNA during asthma pathogenesis and may be a promising therapeutic target to treat allergic airway inflammation.

NADPH Oxidase Dysregulation in Autoinflammatory Osteomyelitis



In this Top Read, Kralova et al. (p. 1607) show that superoxide production by neutrophils drives bone damage in *Pstpip2*^{cmo} mice, a murine model of autoinflammatory osteomyelitis. Neutrophils isolated from the bone marrow of *Pstpip2*^{cmo} mice and stimulated with the inflammasome activator silica showed greater superoxide production compared with neutrophils from wild-type mice. Blockade of IL-1β signaling by deletion of MyD88, which is known to drive autoinflammation in these mice, protected

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them from disease; however, neutrophils from these animals still showed increased superoxide production, indicating that the superoxide dysregulation is not caused by exposure to the chronic inflammatory environment. Increased superoxide production was detectible in asymptomatic 3-wk-old mice, suggesting the increased superoxide production preceded onset of disease. *Pstpip2*^{cmo} mice depleted of neutrophils were protected from disease, highlighting the critical role neutrophils play in the onset of autoinflammation. *Pstpip2*^{cmo} mice lacking NADPH activity were protected from inflammatory bone damage, though inflammation was still present in the soft tissue. The authors showed that PSTPIP2 could bind either PEST-family phosphatases or SHIP1 to suppress protein kinase C–mediated p47phox phosphorylation, attenuating superoxide production. These data indicate that dysregulation of superoxide production in neutrophils is a key factor in promoting bone damage in autoinflammatory disease and may provide a target of future therapeutics.

BAFF Function in Neutrophils and DCs

Despite being essential for B cell development and responses to Ag, little is known about the kinetics governing BAFF production in vivo. In this Top Read, Giordano et al. (p. 1508) created BAFF reporter (BAFF-REP) and *Baff* floxed mice (*Baff*$^{fl/fl}$) to better understand BAFF's functions in B cell responses. Splenic and bone marrow (BM) neutrophils (Nphs) from BAFF-REP mice expressed the highest constitutive levels of BAFF, whereas other myeloid subsets, including conventional dendritic cells (cDCs) and monocytes (MOs), expressed lower levels. Treatment of these mice with Poly(I:C) increased BAFF expression in splenic Ly6C^{hi} MOs, CD11b^{hi} activated NKs, and BM myeloid precursors. Infection of BAFF-REP mice with West Nile virus (WNV) increased BAFF in CD8^{-} cDCs and Nphs and expanded BAFF^{+} CD11b^{hi} NK cells in draining lymph nodes (dLNs). The cell- and tissue-specific increases of BAFF expression were dependent on type I IFN signaling. Mitochondrial activator of virus signaling was required for BAFF expression in DCs, whereas it only contributed to BAFF expression in MO subsets. Selective deletion revealed that BAFF produced by both DCs and Nphs is required for optimal T cell–independent Ag-specific Ab responses. Mice lacking BAFF in cDCs were more susceptible to infection with WNV and had reduced WNV-specific IgG and neutralizing Ab responses. Thus, this study demonstrates that BAFF produced by cDCs is required to protect against lethal virus infection and indicates that BAFF produced by Nphs and cDCs, although regulated differently, has distinct roles in Ab responses and protective immunity.

Role of α2β1 Integrin in NK Cells

This Top Read demonstrates that α2β1 integrin is necessary for optimal NK cell proliferation but is not required for effector function or antiviral responses. Stotesbury et al. (p. 1582) created mice deficient in α2β1 integrin on NK cells, which exhibited normal maturation of NK cells. Additionally, α2β1 deficiency did not alter the NK to innate lymphoid cell balance. In response to ectromelia virus (ECTV) infection, NK cells in mice deficient for α2β1 showed normal accumulation, distribution, and effector function in the LNs. However, α2β1-deficient mice infected with ECTV and mouse CMV (MCMV) showed reduced numbers of NK cells compared with infected wild-type animals, suggesting that α2β1 is necessary for optimal NK cell proliferation. α2β1-deficient NK cells were able to protect mice from high-dose ECTV infection and control spleen MCMV viral titers. These data indicate that although α2β1 integrin may be required for optimal NK cell proliferation, it is not required for acquisition of effector function or antiviral effector function.

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