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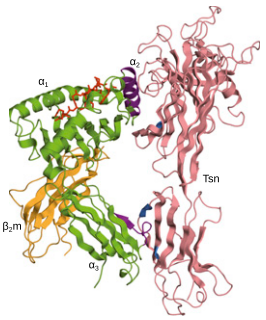
Tapasin Sorts MHC Cargo

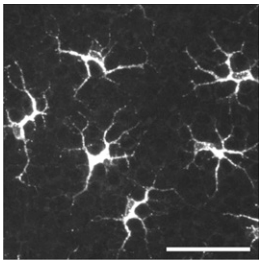


Tapasin (Tsn), a chaperone protein found in the peptide-loading complex in the endoplasmic reticulum, has a key but incompletely understood role in the loading of MHC class I (MHC I) molecules with optimal peptides. In this issue, Fleischmann et al. (p. 4503) determined the structure and dynamics of the Tsn–MHC I interaction at the molecular level. Comparing the association and dissociation rates of low-, medium-, and high-affinity peptides interacting with HLA-B*44:02 in the presence or absence of Tsn revealed that Tsn accelerated the dissociation of the suboptimal peptides (low- and medium-affinity) and catalyzed their exchange for the optimal, high-affinity peptide. Using light to convert a photocleavable high-affinity peptide bound to MHC I into a low-affinity ligand also resulted in Tsn-mediated exchange of these low-affinity ligands for higher affinity peptides. Tsn was found to bind only transiently to MHC I molecules loaded with high-affinity peptides, but to bind with higher affinity once these peptides were converted to suboptimal cargo. All-atom molecular dynamics simulations revealed tighter binding between the N-terminal region of Tsn and the α2 domain of suboptimal peptide-loaded MHC I versus MHC I loaded with high-affinity peptide, and this binding appeared to widen the peptide binding groove and potentially encourage the release of low-affinity ligands. This study delineates a mechanism by which Tsn may interact with some MHC I molecules to control epitope proofreading.

When IgM Autoantibodies Attack

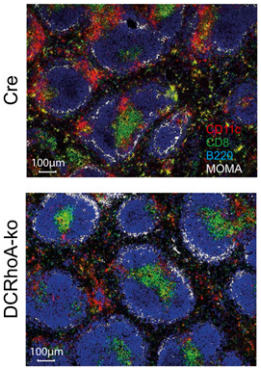
Both IgM and IgG autoantibodies are found in patients with autoimmune anemias and thrombocytopenias, which can develop following viral infections, but the IgG Abs have been more thoroughly studied than the IgM Abs. In mice, anti-platelet IgM Abs can induce thrombocytopenia via phagocytosis of platelets and anti-erythrocyte IgM Abs can cause anemia through a phagocytosis-independent mechanism. It has been shown that IgG autoantibody-mediated induction of anemia and thrombocytopenia can be augmented by infection with lactate dehydrogenase–elevating virus (LDV) via enhancement of macrophage phagocytic activity. Legrain et al. (p. 4171) investigated whether LDV infection similarly affected the pathogenicity of IgM autoantibodies and found that this virus amplified anti-platelet IgM-mediated thrombocytopenia but not anti-erythrocyte IgM-mediated anemia. Macrophages and Fcα/μR, the IgM-binding FcR found on these cells, were necessary for IgM-mediated thrombocytopenia (both with and without LDV infection), but not for IgM-mediated anemia. However, LDV infection did not significantly affect Fcα/μR expression, indicating that viral exacerbation of thrombocytopenia did not require upregulation of this receptor. Taken together, these data indicate that IgM anti-platelet autoantibody-mediated thrombocytopenia requires Fcα/μR on macrophages, but that additional mechanisms exacerbate disease in the context of viral infection.

Lattice of Langerhans Cells



Langerhans cells (LCs), a specialized subset of dendritic cells that patrol the epidermis, establish a network shortly after birth and maintain homeostasis with local precursor proliferation replacing cells that have migrated to the skin draining lymph nodes. Keratinocyte production of IL-34 is required for LC development and Zaru et al. (p. 4264) examined how different kinases activated by the IL-34 pathway affect LC homeostasis. PDK1$^{fl/fl}$/Vav-Cre^{+} mice, which lack PDK1 in the hematopoietic compartment, developed CD11b^{+} dendritic cells but neither LCs nor dermal CD103^{+} dendritic cells. PDK1 activates multiple Ser/Thr kinases including Rsk, of which three isoforms are expressed in LCs. Mice lacking just one isoform had no reduction of LCs, but mice lacking both Rsk1 and Rsk2 (Rsk1/2-null mice) had half the number of LCs as did wild-type (WT) mice. The reduced density was not due to increased LC migration to skin draining lymph nodes, but instead was a result of their reduced proliferative capacity. Although the LCs had normal dendritic morphology and a homogenous distribution, the surface area of the cells was increased, even though activation markers were not. Random sampling of the epidermis of WT and Rsk1/2-null mice showed that LC density and surface area were inversely correlated, leading the authors to hypothesize that the cells were compensating for the diminished network in the epidermis. This hypothesis was supported by the observation that LCs that had migrated to the dermis or lymph nodes had no difference in size. Irradiated WT mice were reconstituted with WT or Rsk1/2-null bone marrow before UV-induced ear inflammation to instigate donor LC migration. Surprisingly, the re-established LC network was similar in cell size and density, regardless of Rsk1/2 expression, indicating that Rsk1/2 are required during ontogeny but not for repopulation following inflammation. These results suggest not only that Rsk is involved in LC development and homeostasis, but also that LCs can increase their surface area in response to reduced numbers in the epidermis.

RhoA Rescues cDCs



At the center of priming adaptive immune responses, conventional dendritic cells (cDCs) need to be tightly regulated to avoid triggering autoimmunity or improper tolerogenic responses. Li et al. (p. 4244) generated DC-specific RhoA-deficient (DCRhoA-ko) mice to investigate the effect on cDC homeostasis of the Rho GTPase RhoA, an enzyme involved in many aspects of cytoskeletal regulation. Although splenic architecture was normal, DCRhoA-ko mice had significantly fewer $CD8^+$ DCs and $CD11b^+Esam^{hi}$ DCs than control mice, whereas $CD11b^+Esam^{lo}$ DCs appeared relatively unaffected by RhoA deficiency. Adoptive transfer experiments revealed blunted priming of Ag-specific T cell responses in DCRhoA-ko hosts. cDC precursors in the bone marrow and spleen of DCRhoA-ko mice were present in normal numbers and able to differentiate into cDCs, suggesting that the decreased number of cDCs was not due to a defective precursor pool. Competitive bone marrow chimeras reconstituted with CD11c-Cre cells and DCRhoA-ko cells demonstrated that the cDC homeostatic defect was DC-intrinsic, as the reconstituted cDC pool was dominated by RhoA-sufficient cells. DCRhoA-ko cDCs were found to have shorter turnover times and increased levels of apoptosis when compared with control cDCs. Proteomic analysis showed that PI3K-γ expression was reduced in DCRhoA-ko bone marrow–derived DCs, and the phosphorylation of the downstream molecules AKT and Bcl-2-associated death promoter (BAD) was also decreased in DCRhoA-ko DC from the bone marrow and spleen, leading to increased apoptosis. Taken together, these results show that RhoA regulates cDC survival by preventing apoptosis.

TRIM38 Trims TLR Inflammation

Toll-like receptor recognition of pathogens initiates a signaling cascade through adaptor proteins to activate transcription factors such as NF-κB and eventually drive production of inflammatory cytokines. The E3 ubiquitin ligase TRIM38 has been shown to inhibit TLR3/4 signaling in cell lines by mediating degradation of TLR adaptor proteins, and Hu et al. (p. 4415) investigated this mechanism in vivo with *Trim38*-knockout ($Trim38^{-/-}$) mice. Following injection of the TLR3 ligand polyinosinic-polycytidylic acid [poly(I:C)] or the TLR4 ligand LPS, $Trim38^{-/-}$ mice had elevated levels of type I IFN, IL-6, and TNF-α as compared with wild-type (WT) mice. Administration of these TLR ligands with D-galactosamine induces inflammatory death, which was exacerbated in $Trim38^{-/-}$ mice. Oral challenge with *Salmonella typhimurium* also resulted in greater weight loss and earlier onset of mortality in $Trim38^{-/-}$ mice than in WT mice. Coimmunoprecipitation experiments demonstrated that Trim38 interacts with the TLR adaptor molecule TIR domain–containing adapter-inducing IFN-β (TRIF), which was supported by the fact that TRIF was relatively upregulated in $Trim38^{-/-}$ bone marrow–derived dendritic cells (BMDCs). Trim38 deficiency reduced poly(I:C)- or LPS-induced polyubiquitination of TRIF, which was dependent on Lys^{228} of TRIF. In WT BMDCs, IFN-β treatment induced Trim38 expression, which led to relatively blunted *Tnfa* and *Il1b* transcription in comparison with $Trim38^{-/-}$ BMDCs, indicating that Trim38 may be involved in a negative feedback loop regulating type I IFN responses. Collectively, these results show that Trim38 targets TRIF to regulate TLR3/4 signaling and downstream inflammatory cytokine production in vivo.