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Top Reads

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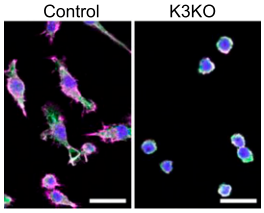
Kindlin-3 Restricts Myeloid Cell Migration

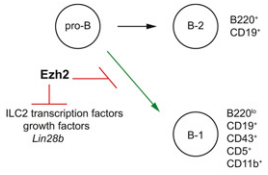


Migration of myeloid cells is mediated by binding with a component of the integrin adhesion complex kindlin-3. In this Top Read, Liu et al. (p. 1954) investigate how Kindlin-3 is incorporated into the adhesion complex, also known as the adhesome, and how its function is regulated. Studies using nuclear magnetic resonance showed that Kindlin-3 directly interacts with paxillin (PXN) and leupaxin (LPXN) via the conserved amino acids G43/L47 within its F0 domain. Disruption of Kindlin-3–PXN/LPXN binding in macrophages via mutations of G43/L47 promoted cell spreading and polarization and inhibited integrin activation, resulting in upregulation of both general cell motility and directed cell migration. In contrast, complete knockout of Kindlin-3 abolished cell adhesion, spreading, and cell polarization. Additionally, disruption of Kindlin-3–PXN/LPXN binding augmented phagocytosis and promoted the transition from mesenchymal migration, which is integrin dependent, to ameboid migration, which is integrin independent. Thus, in contrast to other Kindlin binding partners, interactions between Kindlin-3 and PXN/LPXN negatively regulate integrin-dependent functions of myeloid cells and represent an important mechanism that may impact the pathogenesis of cancer, inflammatory diseases, and degenerative diseases.

Liposome Immunotherapy Suppresses T1D

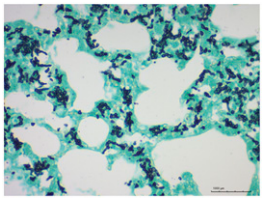
In this Top Read, Bergot et al. (p. 1787) used liposomes to deliver autoantigen epitopes of chromogranin A (ChgA) as an immunotherapy for type 1 diabetes (T1D). Liposomes containing the high-affinity $CD4^+$ mimetope ($BDC2.5_{mim}$) of islet autoantigen ChgA and the NF-κB inhibitor calcitriol induced expansion of BDC2.5 transgenic $CD4^+$ T cells. In vivo, $BDC2.5_{mim}$/calcitriol liposomes induced expansion of endogenous high affinity ChgA-specific $CD4^+Foxp3^+$ T regulatory cells (Treg). ChgA-specific $Foxp3^-CD4^+$ T cells also expanded in mice treated with $BDC2.5_{mim}$/calcitriol liposomes and displayed evidence of Ag experience and effector memory phenotypes. Similar to the Treg populations, the $Foxp3^-$ T cells also produced IL-10 and expressed high levels of ICOS, PD1, and CD73, suggesting that these cells have regulatory potential. Because multiple autoantigens contribute to T1D progression, the authors sought to determine the effects of liposome treatment on nonspecific $CD8^+$ pathogenic T cells. To assess this, NOD mice were treated with $BDC2.5_{mim}$/calcitriol liposomes and islet-specific glucose-6-phosphatase catalytic subunit–related protein (IGRP)–specific $CD8^+$ T cells were transferred following liposome treatment. As expected, ChgA-specific $CD4^+$ Treg cells expanded in these mice, and the IGRP-specific $CD8^+$ T cells decreased in both number and function compared with PBS-treated controls, suggesting that expansion of regulatory $CD4^+$ T cells can suppress pathogenic $CD8^+$ T cells regardless of Ag specificity. Finally, 4 wk of $BDC2.5_{mim}$/calcitriol liposome treatment in hyperglycemic NOD mice delayed diabetes progression and increased survival up to 6 mo. These data demonstrate that liposomes containing islet-specific Ags and calcitriol may provide an improved delivery system for immunotherapy in T1D.

Ezh2 Maintains the B-2 Lineage Fate



Lymphocyte lineage commitment requires concomitant activation of lineage-specific genes and repression of alternative lineage genes. In this Top Read, Jacobsen et al. (p. 1760) tested the requirements for enhancer of zeste homolog 2 (Ezh2), a histone methyltransferase and a catalytic component of the polycomb repressive complex 2 (PRC2) that mediates repression via methylation of histone 3 lysine 27 (H3K27me3), in coordinating B and T lymphocyte gene expression programs. The authors demonstrated that Ezh2 was required in pro-B lymphocytes, but not T lymphocyte progenitors, to maintain repression of numerous growth factors and growth factor receptors, as well as multiple alternative lineage transcription factors, particularly those for T cell and innate lymphoid cell lineages. Ezh2-deficient pro-B cells remained committed to the B cell lineage but diverted to a fetal B-1–like cell phenotype in vitro and in vivo. The diversion of Ezh2-deficent cells to the B-1 fate was associated with a significant increase in the B-1 lineage regulator *Lin28b*, a repressor of the *Let-7* family of microRNAs, and two known *Let-7* target genes. Moreover, the *Lin28b* gene was marked by H3K27me3 in pro-B lymphocytes, indicating that it is a target of PRC2 in adult pro-B cells. Thus, this study reveals a role for Ezh2 in maintaining repression of numerous genes during adult B cell development.

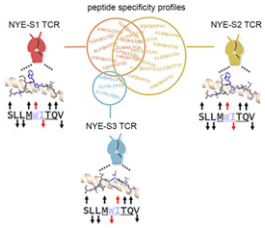
Innate Lung Responses to *Aspergillus* Require 12/15-LOX



In this Top Read, Mackel et al. (p. 1849) demonstrate that 12/15-lipoxygenase (12/15-LOX) is necessary for early innate responses to invasive lung fungal infections. 12/15-LOX–deficient mice ($Alox15^{-/-}$) infected with *Aspergillus*

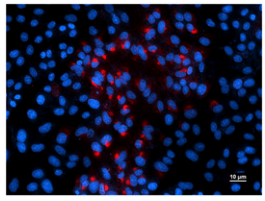
fumigatus exhibited elevated fungal burden and increased lung damage, leading to an 80% mortality rate. Within 6 h of exposure to *A. fumigatus*, there were significant reductions in proinflammatory cytokines and chemokines in the lungs of *Alox15*$^{-/-}$ mice. At this time point, there was also a significant decrease in the number of neutrophils and eosinophils recruited to the lung of *Alox15*$^{-/-}$ mice compared with wild-type controls. However, loss of 12/15-LOX did not affect neutrophil antifungal activity. *Alox15*$^{-/-}$ mice also displayed an intrinsic defect in neutrophil maturation and had fewer metamyelocytes, indicative of a late stage of neutrophil development. 12/15-LOX was also critical for the induction of type 17 responses during *A. fumigatus* infection. Given that prophylactic antifungal protocols have not been efficacious in protecting at-risk patients from invasive *Aspergillus* infections, these data provide a potential target for the development of new therapies.

Off-Target TCR Repertoires



In this Top Read, Coles et al. (p. 1943) elucidate how shared binding footprints and overlapping cross-reactivity profiles contribute to TCR peptide–HLA (pHLA) recognition. The authors assessed the binding strength of three TCRs, NYE_S1, NYE_S2, and NYE_S3, which all bind the same pHLA, and demonstrated that NYE_S1 and NYE_S2 had similar high affinities for pHLA, compared with the lower affinity NYE_S3. Crystal structure analysis of NYE_S1 and NYE_S2 revealed similar binding geometry and peptide conformation, relying predominantly on α-chain peptide interface. This conformation strongly favored recognition of peptides with methionine and tryptophan in the 4 and 5 positions, respectively, protruding from the pHLA surface. NYE_S3, however, showed a unique binding footprint; the β-chain was the major contributor to the peptide interface and, upon binding pHLA, the TCR underwent a conformational change. The authors used phage display libraries encoding 5×10^8 variant peptides bound by HLA to determine off-target peptide recognition. Despite the similar peptide binding geometry of NYE_S1 and NYE_S2, each TCR displayed unique off-target peptide specificity profiles with minimal overlap. The off-target recognition of NYE_S3 had almost no overlap with NYE_S1, NYE_S2, or the native peptide, further demonstrating that NYE_S3 engages a different conformational epitope. Together, these data indicate that TCRs recognizing similar epitopes also display nonoverlapping specificity profiles. As engineered TCRs are increasingly used clinically, it will become important to understand off-target TCR repertoires and their potential impact on the safety of TCR-based immunotherapy.

AMPK Activation Attenuates Zika Virus Replication



Recent studies have demonstrated that Zika virus (ZIKV) substantially enhances cellular metabolism of infected cells. In this Top Read, Singh et al. (p. 1810) investigated the role of AMP-activated protein kinase (AMPK), a master regulator of energy metabolism, in response to ZIKV infection. ZIKV infection of endothelial cells caused a time-dependent reduction of active AMPK and its downstream target acetyl-CoA carboxylase. Activation of AMPK attenuated ZIKV infection, and this effect was reversed by the addition of an AMPK inhibitor. Endothelial cells deficient in AMPK were permissive to ZIKV infection, demonstrating a role for this kinase in regulating innate antiviral immunity. Consistent with these observations, AMPK activation potentiated the expression of antiviral genes such as *IFNs, OAS2, ISG15,* and *MX1* and inhibited inflammatory mediators such as *TNF-α* and *CCL5*. Additionally, bioenergetic analysis of endothelial cells demonstrated that ZIKV infection elevated extracellular acidification rate levels and increased expression of key glycolytic genes, whereas activation of AMPK reduced this response. Finally, inhibition of glycolysis augmented AMPK activity and attenuated ZIKV infection. Thus, this study reveals a role for AMPK in regulating the innate antiviral response and glucose metabolism of endothelial cells during ZIKV infection