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Top Reads

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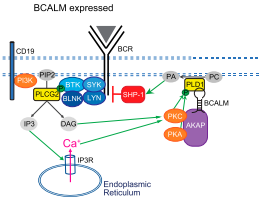
lncRNA Modulates BCR Ca^{2+} Signaling

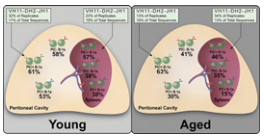


In this Top Read, Pyfrom et al. (p. 595) functionally characterized a human B cell–specific long noncoding RNA (lncRNA) that had high levels of expression in normal B cells and three types of B cell cancer. The authors identified *AC099524.1*, named B cell–associated lncRNA modulator of BCR-mediated Ca^{2+} signaling (BCALM), upstream of the gene encoding phospholipase C γ 2, a B cell–specific enzyme that stimulates intracellular Ca^{2+} signaling in response to BCR activation. Studies identified phospholipase D 1 (PLD1), as well as kinase adaptors AKAP9 and AKAP13, as BCALM-interacting proteins. Together, these factors form signaling complexes to aid in the phosphorylation and activation of PLD1 and production of phosphatidic acid (PA). Relative to wild-type cells, BCR stimulation of BCALM-deficient B cells showed decreased PLD1 phosphorylation and increased intracellular Ca^{2+} flux. These data suggest that BCALM negatively feeds back to downmodulate BCR-mediated calcium signaling via phosphorylation of PLD1 by AKAP-associated kinases, thereby enhancing production of PA. Because PA activates SHP-1, which negatively regulates BCR signaling, these findings provide a new paradigm for lncRNA-mediated modulation of B cell activation and signaling.

Glucocorticoids Regulate B Cell Migration

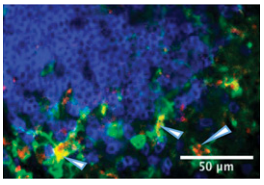
Whereas glucocorticoids are known to promote CXCR4 expression by numerous immune cell types, it is unknown if they regulate CXCR4 expression in B cells. In this Top Read, Cain et al. (p. 619) demonstrated that glucocorticoids upregulated CXCR4 mRNA and protein in murine B cells. Reduced expression of CXCR4, associated with B cell–specific glucocorticoid receptor (GR) deficiency, impaired homing of mature B cells to the bone marrow (BM) but did not impact their migration to other lymphoid tissues. GR-deficient B cells also lacked the circadian rhythmicity normally associated with glucocorticoid secretion, suggesting that movement of mature B cells between blood and BM is sensitive to small, physiological changes in glucocorticoid activity. Furthermore, mice with a B cell–specific deletion of GR mounted normal humoral responses toward T-dependent and T-independent Ags, whereas Ab responses toward multivalent T-independent Ags were impaired. Thus, the authors propose that endogenous glucocorticoids regulate B cell migration between the blood and BM, possibly as a mechanism of enhancing humoral immunity during diurnal periods of activity.

Age and Location Influence Natural IgM Repertoires



Natural Ig, which is germline-like due to minimal N-region insertions, is produced by B-1a cells. Because natural IgM plays a vital role within the immune system, Tsuji et al. (p. 741) sought to understand how B-1a derived natural IgM changes with age. Previous work demonstrated that peritoneal B-1a cell–derived phosphorylcholine (PC)-specific IgM and total IgM move away from germline with age. In this Top Read, the authors demonstrated that anti-phosphatidylcholine (PtC)–specific peritoneal B-1a cell IgM Abs are germline-like and do not change with age. In contrast, splenic PtC-binding B-1a cells did not preserve IgM germline status in aged mice and displayed more diverse V_H repertoires in both young and aged mice. Whereas the peritoneal PtC-binding population increased V_H12 use with age, the authors observed differential use of V_H11, V_H12, and V_H2 between the peritoneal and splenic PtC-binding populations with age, suggesting disparate selection pressures related to age and anatomical location. Thus, Ag specificity and location of B-1a cells determines how the population is impacted by age and selection over time and, therefore, may aid in the development of more effective vaccination and therapeutic strategies in aged populations.

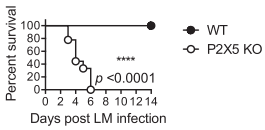
B Cell Activation by DC Regurgitation



To initiate humoral immune responses, dendritic cells (DCs) present Ag to B cells within the follicular region of secondary lymphoid organs. In this Top Read, El-Barbry et al. (p. 608) sought to further elucidate the mechanisms by which DCs facilitate Ag transfer and B cell activation. Murine DCs transported Ag from the periphery to the lymph node B cell zone, where they facilitated B cell activation. Activation of B cells was due to extracellular release of Ag by DC regurgitation rather than by cell-to-cell contact. Furthermore, Ag release by DC regurgitation induced early B cell activation that was BCR driven and was associated with sustained nuclear accumulation of NF-κB/c-Rel. Consistent with these observations, chemical inhibition of c-Rel blocked both early B and T cell activation specifically induced upon stimulation of Ag receptors. Thus, this study provides new insight into the mechanisms by which DCs deliver Ag to and activate B cells. Importantly, the data

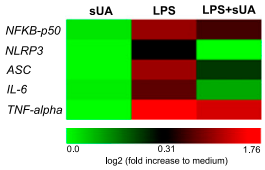
suggest that therapeutic targeting of the NF-κB/c-Rel pathway may limit excessive DC-elicited B/T cell responses in autoimmunity without altering the host humoral defense against bacterial infections.

P2X5 Activates Inflammasomes during *Listeria* Infection



In this Top Read, Jeong et al. (p. 760) established a role for the ligand-gated cation channel, P2X5, in protective immunity against *Listeria monocytogenes*. Compared with wild-type mice, those deficient in P2X5 ($P2X5^{-/-}$) had greater bacterial burdens, extensive liver damage, and higher mortality following *L. monocytogenes* infection. P2X5 deficiency, however, did not affect expression of IL-12 or IFN-γ, nor did it impact monocyte recruitment, all of which are essential components of the immune response to *L. monocytogenes*. Based on previously reported functions of other P2X receptors, the authors investigated the effects of P2X5 on bone marrow–derived macrophages (BMM) and showed that BMMs from $P2X5^{-/-}$ mice had reduced killing capacity in vitro. Additionally, infection of $P2X5^{-/-}$ BMMs decreased caspase-1 activation and reduced levels of mature IL-1β, suggesting that P2X5 is required for inflammasome activation in response to *L. monocytogenes*. Direct chemical activation of inflammasomes rescued *L. monocytogenes* killing in $P2X5^{-/-}$ BMM, further supporting a role for P2X5 in *L. monocytogenes*-mediated activation of inflammasomes. Surprisingly, P2X5 did not use conventional extracellular ATP-mediated signaling, which is required by other P2X receptors. Together, these data demonstrate a role for P2X5 in *L. monocytogenes*–induced inflammasome activation.

Uric Acid Suppresses Tissue Inflammation



Monosodium urate (MSU) crystals trigger acute inflammation and are the cause of gouty arthritis. Soluble uric acid (sUA), the substrate for the formation of MSU crystals, has varying and conflicting immune effects reported in the literature. In this Top Read, Ma et al. (p. 789) demonstrated that different preparation methods, prewarming and solubilization with sodium hydroxide (NaOH), affect the ability of sUA to inhibit MSU crystal–induced tissue inflammation. Prewarmed sUA contained microcrystals that triggered the release of IL-1β from THP-1 cells, a human peripheral blood cell line. sUA solubilized with NaOH, however, was free of microcrystals and did not appear to have any proinflammatory properties. Injection of MSU crystals into hyperuricemic mice decreased recruitment of $CD45^+$ cells, monocytes, and neutrophils, and reduced levels of IL-1β and IL-6, suggesting that increased levels of sUA in the blood attenuates MSU crystal–induced inflammation. Stimulation of healthy human $CD14^+$ monocytes with either LPS or MSU crystals resulted in cellular activation, which was suppressed by preincubation with sUA. Compared with monocytes from healthy patients, stimulation of monocytes from patients with hyperuricemia reduced activation. The urate reabsorption transporter SLC2A9 was found to be selectively expressed on human $CD14^+$ monocytes and THP-1 cells, silencing of which abolished the suppressive effect of sUA on LPS-activated monocytes. These data provide evidence that sUA has anti-inflammatory effects and suggest that previous studies reporting inflammatory effects of sUA are likely due to contamination during their preparation.

Pig Model for Ab Therapy

In this Top Read, McNee et al. (p. 648) demonstrated the utility pigs serve as a model for accurately predicting the efficacy of influenza Ab therapy in humans. Compared with isotype or diluent controls, pigs treated prophylactically with the protective human neutralizing mAb 2-12C had decreased viral loads in both nasal swabs and bronchoalveolar lavage (BAL) when challenged with the pandemic swine H1N1 isolate (pH1N1). Additionally, virus was not detected in the lungs of the 2-12C treated pigs and this correlated with significantly improved histopathological scores when compared with either control group. DNA plasmid encoded mAb (dMAb) 2-12C injected into the muscle of pigs using electroporation resulted in local expression of 2-12C. Compared with pigs receiving 15 mg/kg 2-12C i.v., those receiving dMAb 2-12C treatment prophylactically did not show a reduced viral load in the nasal swab or BAL. However, compared with control treated animals, those receiving dMAB 2-12C treatment had significantly reduced viral load in the lung at 4 d postinfection. Importantly, histopathological scores were decreased across all experimental groups. Overall, these data demonstrate that mAb 2-12C is a good candidate for influenza Ab therapy, and that the pig is a useful model to study Ab effectiveness toward viral infections.