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Top Reads

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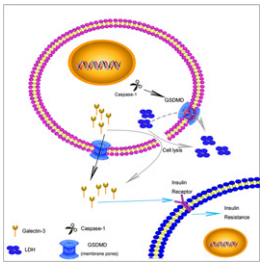
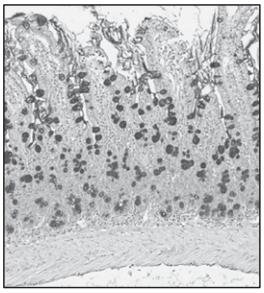
The Inflammasome–Galectin-3 Axis Mediates Insulin Resistance



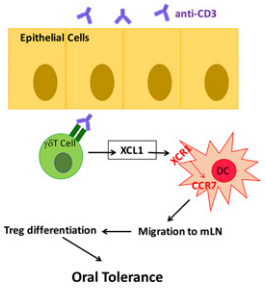
Although the function of the NLRP3 inflammasome has been attributed largely to the activity of IL-1β, several studies have suggested the existence of additional downstream effector molecules. In this Top Read, Chen et al. (p. 2712) identified galectin-3 as an NLRP3-regulated secretory protein using an unbiased secretome screen. Additional studies demonstrated that active gasdermin D drives the secretion of galectin-3 through the plasma membrane pores, independent of the exosome pathway. In addition, the authors sought to elucidate the mechanisms connecting galectin-3 and inflammasome activation to insulin resistance. In vivo, mice deficient in NLRP3 (*Nlrp3*$^{-/-}$) fed a high-fat diet exhibited decreased circulating galectin-3. Additionally, these mice had decreased blood glucose levels and displayed enhanced insulin sensitivity when compared with wild-type controls, suggesting that inflammasome-associated insulin sensitivity is mediated by galectin-3. Consistent with these observations, administration of recombinant galectin-3 aggravated insulin resistance in obese *Nlrp3*$^{-/-}$ mice. Thus, this study identifies galectin-3 as a functionally important effector molecule downstream of inflammasome activation that impairs insulin signaling and suggests that the inflammasome–galectin-3 axis may be a promising target for therapeutic intervention in the treatment of diabetes.

Inflammasome-Independent Role for NLRP3 in Helminth Infection



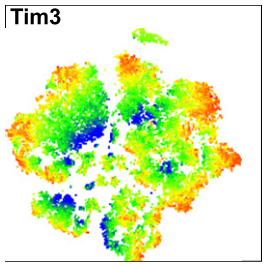
This Top Read suggests an inflammasome-independent role for NLRP3 in type 2 immune responses and lung repair following helminth infection. NLRP3 has been widely studied in the context of classically activated macrophages (Mφs). To determine the contribution of the NLRP3 inflammasome in the function of alternatively activated Mφs, Chenery et al. (p. 2724) infected NLRP3-deficient (*Nlrp3*$^{-/-}$) mice with *Nippostrongylus brasiliensis* and assessed acute lung injury, innate immune cell activation, and lung repair. The authors found that *Nlrp3*$^{-/-}$ mice infected with *N. brasiliensis* had increased protective innate responses characterized by increased early IL-4 expression, an increase in recruitment of neutrophils and eosinophils to the lung, and a decrease in lung-stage L4 larvae. However, this innate response was prolonged when compared with wild type (WT) mice. Increased expression of Ym1 at day seven postinfection, along with extended recruitment of neutrophils, and persistent cellular inflammation in the airways, exacerbated lung damage and prolonged tissue repair. Comparison of gene expression in infected *Nlrp3*$^{-/-}$ versus WT mice provided further evidence of dysregulated type 2 gene expression in *Nlrp3*$^{-/-}$ mutants. Finally, the lack of infection-induced pro–IL-1β or caspase-1 produced by alveolar Mφs, along with a lack of mature IL-1β in airways, suggested that the role of NLRP3 in *N. brasiliensis* infection is inflammasome independent. These data demonstrate a new and exciting role for NLRP3 in the type 2 responses of parasitic lung infections.

γδ T Cells Mediate Anti-CD3–Induced Oral Tolerance



The induction of oral tolerance has classically involved oral administration of Ags. However, recent studies have shown that oral administration of anti-CD3 mAb induces tolerance in several animal models of autoimmune and inflammatory diseases via the generation of regulatory T (Treg) cells. In this Top Read, Rezende et al. (p. 2621) demonstrate that oral administration of anti-CD3 induces migration of intestinal type 1 conventional dendritic cells (cDC1) and that depletion of cDCs completely abrogates the induction of oral tolerance in the murine experimental autoimmune encephalomyelitis (EAE) model. Oral anti-CD3 administration was found to promote secretion of XCL1 in small intestine lamina propria (SLIP) γδ T cells, which in turn induced migration of XCR1^{+} DCs to the mesenteric lymph node. Interestingly, XCL1 was not required for oral tolerance induced by fed Ags, suggesting a different immune pathway for the induction of tolerance. However, oral administration of anti-CD3 enhanced oral tolerance induced by fed MOG_{35-55} peptide, resulting in less severe EAE and increased Treg cells in the spleen. Thus, induction of Treg cells by oral anti-CD3 is driven by γδ T cells and tolerogenic DCs in the intestine. Furthermore, anti-CD3 may be used as an adjuvant to enhance oral tolerance to fed Ags for the treatment of autoimmune diseases.

Impact of MSCs on Tumor Growth



This Top Read demonstrates that mesenchymal stromal cells (MSC) do not promote tumor growth, nor do they interfere with tumor rejection. Despite their use in multiple clinical trials, the heterogeneity of MSCs has led to confounding reports of their biological properties and concerns regarding tumor promotion. Moquin-Beaudry et al. (p. 2735) use humanized mouse models to investigate the role of MSC on fibroblastic tumor growth. In the first model, humanized mice were created by transferring human WBCs into NSG-SGM3 (human adoptive transfer [Hu-AT]) mice. In both solid and metastatic tumor models, MSC treatment did not increase the tumor size or alter the ability of autologous human immune cells to prevent or delay tumor growth. Flow cytometry analysis of blood and tumor microenvironments demonstrated that the immune cell landscape is altered by the tumor itself, but not the presence of MSC. In a second model, cotransplantation of human fetal liver hematopoietic stem cells and autologous fetal thymus tissue into NSG (human BLT [Hu-BLT]) mice generated a humanized mouse model with continuous renewal of functional T cells. Consistent with results observed in the Hu-AT mice, MSC treatment did not alter the ability of Hu-BLT mice to completely or partially eliminate tumors. However, the immune landscape of the Hu-BLT mice was somewhat altered by injection of MSC, wherein tumor-infiltrating T cell populations had a significant increase in the percentage of $CD8^+$ T cells and a significant decrease in the percentage of regulatory T cells. Together, these data support the safety of MSC therapies, as they are unlikely to promote secondary tumor growth.