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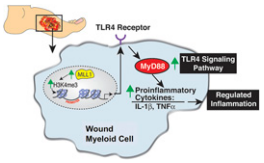
TLR4 Mediates Inflammation in Early Wound Healing

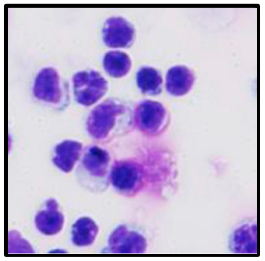


Wound healing is a complex process that is tightly regulated by myeloid cells. Whereas recent studies have demonstrated the importance of TLR4 in the regulation of myeloid-mediated inflammation, Davis et al. (p. 1777) sought to elucidate the role of TLR4 in early cutaneous wound healing. When compared with wild-type (WT) controls, the wounds of TLR4-deficient (*Tlr4*$^{-/-}$) mice showed impaired epithelialization and decreased collagen content, which are indicative of impaired wound healing. Additionally, myeloid-derived cells from *Tlr4*$^{-/-}$ mice expressed reduced levels of IL-1β and TNF-α, which are known to be important during early wound healing. Delayed wound healing and decreased inflammatory cytokine production was also seen in MyD88-deficient (*Myd88*$^{-/-}$) mice, indicating the importance of MyD88-dependent TLR4 signaling in early wound healing. Adoptive transfer of monocytes and macrophages from WT mice into *Tlr4*$^{-/-}$ animals demonstrated that TLR4 expression by myeloid-derived cells was sufficient to rescue wound healing. Finally, the authors showed that TLR4 expression in myeloid cells was regulated epigenetically via the histone methyltransferase mixed-lineage leukemia 1 (MLL1). Consistent with these observations, TLR4 expression was significantly decreased in myeloid-specific Mll1 (*Mll1*$^{f/f}$*Lyx2*$^{Cre+}$) knockout mice compared with their littermates. Consequently, *Mll1*$^{f/f}$*Lyx2*$^{Cre+}$ mice also exhibited diminished wound healing. Together, these data suggest that therapeutic targeting of the MyD88-dependent TRL4 pathway may enhance wound healing.

Type 1 IFN and Childhood Asthma

Although it is known that respiratory viral infections are the leading cause of asthma and wheezing exacerbations, the underlying mechanisms in susceptible children are not well understood. Khoo et al. (p. 1845) used a systems biology approach to determine the role of gene expression networks in these exacerbations. Pathway analysis of microarray data using nasal swab specimens from children presenting with wheezing in the emergency department (ED) revealed an upregulation of type I IFN signaling when compared with healthy controls. Cluster analysis of data from wheezing children showed that the majority (80%) of children were in one of two clusters based on expression levels of IFN regulatory factor (IRF) 7, a master regulator of type 1 IFN. IRF7^{hi} subjects showed an increased expression of type 1 IFNs pathways, whereas IRF7^{lo} subjects showed increased Th-2 signaling pathways. Clinical characteristics of the IRF7^{hi} and IRF7^{lo} populations were also significantly different; compared with the IRF7^{hi} group, the IRF7^{lo} group showed symptoms for a longer period of time before presenting to the ED. Additionally, the IRF7^{lo} children were 4.6 times more likely to be admitted to the hospital for additional care and were more likely to present in the ED with additional exacerbations within a year. Therefore, this study demonstrates a role for the IRF7 gene cluster in clinical asthma presentations.

L-Citrulline and Lung Defense



Active *Mycobacterium tuberculosis* infection is associated with reduced systemic L-arginine levels (L-ARG), which can have detrimental effects on macrophage and T cell responses. Lange et al. (p. 1747) now examine the role of L-citrulline (L-CIT) metabolism in the *M. bovis* bacillus Calmette–Guérin (BCG) model of murine tuberculosis infection. L-CIT can be metabolized from L-ARG and can be used to synthesize L-ARG, depending on the metabolic enzymes involved. In this issue, the authors compared amino acid levels and observed that L-ARG increased moderately in the lung and systemically during infection. By comparison, L-CIT rose dramatically at early times postinfection, then decreased, and these fluctuations were not detectable systemically. Myeloid cells from infected lungs showed increased expression of genes involved in L-CIT metabolism. The genes *Ass1* or *As1*, needed for L-ARG synthesis from L-CIT, were required to control pulmonary infection by *M. bovis* BCG or *M. tuberculosis* $H_{37}R_v$. These results highlight the importance of amino acid metabolism in host defense against mycobacterial disease.

Fully Functional NK Cells

Tyrosine kinase 2 (TYK2) regulates multiple signaling pathways involved in cytokine expression by a number of immune cell types. In this issue, Simonović et al. (p. 1724) examine the role of TYK2 in NK cell cells using conditional ablation. NK-specific deletion of TYK2 does not alter NK cell maturation in mice. In contrast, TYK2-deficient CD11c^{+} cells have lower surface expression of IL-15Rα and hinder NK cell development, but this defect can be overcome with exogenous IL-15/IL-15Rα treatment. NK cell expression of TYK2 is needed for IL-12 signaling and protection against *Listeria monocytogenes* but is not required for cytotoxic or antitumor functions. Defective IFN-γ production in *Tyk2*$^{-/-}$ NK cells correlated with greater methylation on the *Ifng* promoter. Together, these results better define the role of TYK2 in NK cell development and function.