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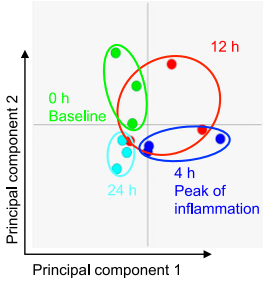
The Journal of Immunology

Resolving an Aging Conundrum



The resolution of inflammatory responses, which is important to avoid collateral damage following infection or injury, is an active process involving several families of lipid mediators collectively designated specialized proresolving mediators (SPMs). Aging is associated with a generalized inflammatory state, which Arnardottir et al. (p. 4235) hypothesized could result from dysregulation of SPMs. They found that, relative to young mice, aged mice demonstrated enhanced inflammation and delayed inflammatory resolution, accompanied by defects in clearance of apoptotic PMNs, following induction of self-limiting acute inflammation through i.p. injection of zymosan. Analysis of metabololipidomic profiles of young versus aged mice revealed that aged mice had increased proinflammatory lipid mediators and decreased SPMs both before and after inflammatory challenge, along with delayed SPM upregulation during inflammation. Treatment of mice with the SPM precursor docosahexaenoic acid (DHA) accelerated inflammatory resolution and increased SPM levels, and DHA could also reprogram human monocytes to acquire a proresolving phenotype. Finally, the authors developed humanized nano-proresolving medicines (NPRMs) to allow localized delivery of the SPMs D-series resolvin (RvD) 1 and RvD3 and found that these RvD NPRMs significantly enhanced inflammatory resolution in aged mice. These results both identify aging-related defects in the resolution of inflammation and propose treatments that may effectively counter these deficiencies.

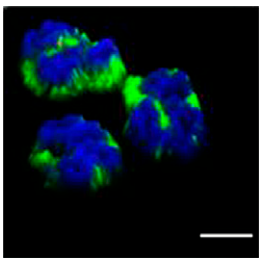
IL-33's Expansive Power

IL-33 is an IL-1 family member that can curb inflammatory responses, most likely by promoting expansion of $Foxp3^+$ regulatory T cells (Tregs) through engagement of the IL-33 receptor ST2. The mechanism and cells involved in this IL-33–driven process are not completely clear, and Matta et al. (p. 4010) now show that IL-33 can stimulate $CD11c^+$ dendritic cells (DCs) to produce IL-2, which in turn promotes expansion of $ST2^+$ Tregs. They observed that ~10% of $CD3^+CD4^+CD25^+$ T cells in the thymus and spleen of naive mice also coexpressed ST2 and Foxp3, and IL-33 treatment expanded this pre-existing T cell population in the spleen. In vitro assays showed that IL-33–expanded $ST2^+$ Tregs potently suppressed the proliferation of $CD4^+$ and $CD8^+$ T cells, and these Tregs also curbed IL-33–driven IFN-γ production by $CD8^+$ T cells. $CD11c^+$ DCs produced significant amounts of IL-2 during IL-33 stimulation, and IL-2 from these DCs induced expansion of $ST2^+$ $Foxp3^+$ T cells. In line with this in vitro data, mice depleted of $CD11c^+$ DCs and treated with IL-33 failed to expand $ST2^+$ $Foxp3^+$ Tregs. Together, these findings indicate that $CD11c^+$ DCs and IL-2 signaling are critical to $ST2^+Foxp3^+$ Treg expansion during exposure to IL-33, thus contributing to a potent anti-inflammatory response.

Down Syndrome's *AIRE* Condition

Down syndrome (DS), a genetic disorder also known as trisomy 21, is associated with a wide range of abnormalities, including a high incidence of autoimmune disorders. Giménez-Barcons et al. (p. 3872) examined how decreased expression of the autoimmune regulator protein (*AIRE*) and peripheral tissue-restricted Ags (TRAs) in DS thymii contribute to this autoimmune tendency. *AIRE* is a transcription factor expressed in thymic medullary epithelial cells and is important for the induction of central tolerance to self. Expression of *AIRE* mRNA was significantly reduced in the thymic tissue of DS subjects relative to controls, although expression from all three *AIRE* copies, due to trisomy, was confirmed. *AIRE* is a key component driving intrathymic expression of TRAs through a process called promiscuous gene expression (pGE), and quantitative PCR analysis revealed that several *AIRE*-dependent TRAs were expressed at significantly lower levels in the thymic tissue of DS subjects relative to controls. DS is associated with a greater incidence of thyroid disease, and in this study, DS individuals who had developed hypothyroidism also had significantly reduced intrathymic expression of *AIRE* and thryoglobulin, a thyroid autoimmune target whose intrathymic expression is Aire-dependent. Together these results affirm that *AIRE* expression is significantly reduced in DS subjects, which impacts pGE and is likely to play a key role in contributing to autoimmunity.

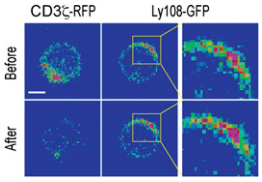
Accelerating Apoptosis in AATD



The protease inhibitor alpha-1 antitrypsin (AAT) blocks serine proteases, including neutrophil elastase, and hereditary AAT deficiency (AATD) results in severe inflammatory lung disease that involves the activity of neutrophils. In this issue, Hurley et al. (p. 3978) assessed whether alterations in neutrophil apoptosis played a role in lung disease and in the effectiveness of AAT augmentation therapy in individuals with AATD (ZZ-AATD). Compared with cells from healthy controls, ZZ-AATD neutrophils had increased expression of markers of apoptosis and endoplasmic reticulum (ER) stress, which was associated with accumulation of mutant AAT protein in the ER. These cells also underwent augmented

apoptosis via the external death pathway, which correlated with increased activity of ADAM-17 and release of soluble TNF-α from the cell surface. In vitro treatment of both ZZ-AATD and control neutrophils with physiologically relevant concentrations of AAT reduced apoptosis and ADAM-17 activity, suggesting a mechanism by which AAT augmentation therapy might reduce lung inflammation. Indeed, analysis of neutrophils from AATD patients following treatment with AAT revealed downregulation of ADAM-17 and caspase activity, resulting in decreased apoptosis. However, no changes were observed in markers of ER stress, suggesting that control of apoptosis was achieved through a mechanism involving ADAM-17 and TNF-α. ZZ-AATD neutrophils were shown to have impaired bactericidal activity, and this impairment could also be reversed by AAT augmentation therapy. This translational study provides insight into the role of AAT in preventing apoptosis in neutrophils and suggests a mechanism through which AAT augmentation therapy ameliorates manifestations of AATD.

SAP-ing the Strength of T–B Adhesion



The intracellular adaptor protein signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) is expressed in T cells and is required for the interactions between T and B cells that are necessary for germinal center responses. To resolve some confusing data regarding the involvement of the SLAM family molecule Ly108 in SAP-regulated T cell–B cell adhesion, Chu et al. (p. 3860) systematically analyzed the actions of SAP and Ly108 during T cell activation. SAP was found to be necessary for T–B adhesion as early as 5 min after Ag recognition; however, the only SAP motif required to support this adhesion was the phosphotyrosine-binding groove of the SH2 domain. Expression in SAP-sufficient or -deficient T cells of Ly108, but not SLAM or CD84, impaired B–T interactions, with a particularly notable effect in the absence of SAP. Ly108 also inhibited cognate interactions between SAP-deficient T cells and dendritic cells, and in activated T cells, Ly108 constitutively interacted with the phosphatase SHP-1. Through a mechanism requiring its cytoplasmic domain, Ly108 colocalized with the CD3 complex and impaired CD3ζ phosphorylation in vitro and inhibited interactions between $SAP^{-/-}$ T cells and B cells in vivo. Transengagement of Ly108 resulted in aggregation of this molecule with CD3ζ through a mechanism requiring the Ly108 transmembrane domain, and crosslinking of Ly108 on $SAP^{-/-}$ T cells resulted in CD3ζ dephosphorylation. Taken together, these data identify two mechanisms by which Ly108 colocalizes with CD3ζ to negatively regulate TCR signaling, leading to downstream impairment of T–B adhesion in the absence of SAP.

Eosinophil Exploitation and Parasite Preservation

Eosinophils are thought to play a role in promoting the growth and survival of the intracellular parasite *Trichinella spiralis* in muscle, but the mechanism involved in this process has not been clearly discerned. Huang et al. (p. 4178) describe how eosinophils downregulate local NO production at the site of *T. spiralis* infection, which is required for long-term survival of parasite larvae. Mice deficient in arginase I in myeloid cell populations showed increased NO-driven larval killing relative to wild-type mice although larvae grew normally, indicating that NO toxicity is specific to larval killing. Eosinophils were recruited early and rapidly to the sites of infection in muscle and produced IL-10, which promoted expansion of $IL\text{-}10^{+}$ myeloid dendritic cells (mDCs) and $CD4^{+}IL\text{-}10^{+}$ T cells. This early eosinophil recruitment was pivotal to suppressing local NO production by inhibiting *iNOS* expression, which supported long-term larvae survival. Eosinophils did not need to be able to present Ag or produce IL-4 to prevent larval killing, further revealing the importance of IL-10 in regulating NO production. These results expose a unique immune strategy of eosinophil exploitation by *T. spiralis* to maintain the long-term survival of parasites in muscle tissue.