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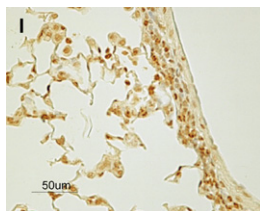
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Smoke Stifles Prenatal Lungs

Secondhand cigarette smoke (SS) has been shown to put children at greater risk for developing allergic asthma and respiratory infections. Singh et al. (p. 4542) examined the influences of prenatal or early postnatal SS exposure in a murine allergic asthma model to better define how SS affects lung function and asthma development. Pregnant mice or their offspring were exposed to SS during gestation and/or 8 to 10 weeks after birth to examine various effects of SS exposure. Prenatal SS exposure was associated with significantly greater airway resistance induced by methacholine or *Aspergillus fumigatus* relative to control mice exposed to filtered air. In addition, prenatal SS exposure correlated with increased serum IgE and activation of Th2-polarizing signals in lung tissue, as well as significantly greater Th2 cytokine levels and leukocyte infiltration in the lungs. Postnatal SS exposure did not result in similar changes. Interestingly, prenatal and/or postnatal SS exposure inhibited expression of the Th1-specific transcription factor T-bet and resulted in suppression of mucus production, goblet cell metaplasia, and expression of mucus-related molecules. These results suggest that prenatal SS exposure can predispose children to asthma and infection due to augmented Th2 polarization and defects in lung development and mucus production.



Ras Revelation in the Thymus

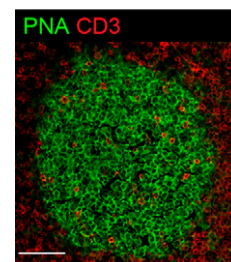
During TCR β -chain selection, double negative thymocytes that express a pre-TCR complex are able to undergo further selection, which eventually results in the development of CD4⁺CD8⁺ double positive thymocytes. Interestingly, thymocytes expressing a constitutively active form of the GTPase Ras or a Ras activator can develop into double positive thymocytes in the absence of a pre-TCR, suggesting a role for Ras signaling during TCR β -chain selection. Janas and Turner (p. 4667) show that an interaction between Ras and the p110 γ subunit of PI3K is required for TCR β -chain selection. Mice engineered to express a mutant form of p110 γ that is unable to interact with Ras had a partial block in TCR β -chain selection. The interaction between Ras and p110 γ was shown to promote proliferation but did not affect thymocyte differentiation or survival. Moreover, active Ras was required to interact with p110 γ for optimal CXCR4-mediated PI3K signaling and thymocyte proliferation during TCR β -chain selection. These data reveal new insights into the mechanism by which Ras influences TCR β -chain selection and thymocyte signaling by interacting with p110 γ .

RNA Sensor Revealed

Innate immune responses against viral infections can be triggered by intracellular detection of viral RNA or DNA via pattern recognition receptors. Zhang et al. (p. 4501) define a role for the DExDc helicase family member, DHX9, as a sensor of viral dsRNA in myeloid dendritic cells (mDCs). Previous studies identified two dsRNA-binding motifs (DSRMs) in DHX9 and characterized it as a MyD88-dependent microbial sensor that activates NF- κ B responses in plasmacytoid DCs. In this study, short-hairpin RNA knockdown of DHX9 in mDCs significantly reduced production of inflammatory cytokines and type I IFN in response to DHX9-specific recognition of polyinosine-polycytidylic acid (poly I:C), a viral dsRNA mimic, or reovirus or influenza virus infection. Further in vitro analysis confirmed that DHX9 could bind to poly I:C via its DSRMs, and another set of domains in DHX9 interacted with CARD domains in IPS-1, an adapter protein involved in viral RNA sensing. In addition, short-hairpin RNA-mediated knockdown of DHX9 or IPS-1 significantly reduced NF- κ B and type I IFN signaling in response to poly I:C stimulation of mDCs compared with controls. Thus, these observations suggest that DHX9 is a dsRNA sensor that interacts with IPS-1 to trigger innate antiviral responses.

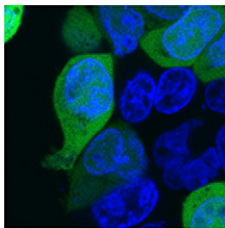
Regulation Center

germinal centers (GCs) are the site for multiple processes that support the development of high affinity Ag-specific memory B cells and plasma cells. Follicular T helper (T_{FH}) cells have been shown to interact with B cells in GCs, and Wollenberg et al. (p. 4553) show that a subset of T_{FH} cells are key regulators of the GC reaction (GCR). A subpopulation of Foxp3⁺ follicular T cells was detected in GCs of OVA-immunized mice. These cells expressed high levels of the regulatory T cell (Treg) markers CD25, CD103, and GITR, as well as the T_{FH} cell markers CXCR5 and PD-1 and the transcription factor Bcl-6. The proliferation rate and density of the Foxp3⁺ follicular T cells peaked in the GC at ~12 days postimmunization, which correlated with the peak of the GCR. Further investigation indicated that the Foxp3⁺ follicular T cells originated from natural Tregs. CXCR5-deficient Foxp3⁺ T cells, which are unable to enter GCs, were transferred into TCR α ^{-/-} mice that lack natural Tregs, resulting in significantly larger GCs and higher Ab titers, compared with mice given wild-type Tregs. Taken together, these data indicate that Foxp3⁺ follicular T cells in GCs regulate the kinetics and amplitude of the GCR and help prevent uncontrolled GCRs, which are associated with cancer and autoimmune diseases.



IL-1's Order of Operations

The immune system is alerted to damage caused by tissue injury-related hypoxia by the release of molecules from hypoxic cells. The family of IL-1 cytokines has many pro-inflammatory effects. In this issue, Rider et al. (p. 4835) showed that IL-1 α and IL-1 β have different impacts on the recruitment of myeloid cells and duration of inflammatory responses triggered by hypoxic cell products. Using a mouse model of sterile inflammation, leukocyte infiltration was measured in Matrigel plugs loaded with different keratinocyte lysates. Significantly more leukocytes infiltrated plugs containing hypoxic lysates compared with control normoxic lysates. Moreover, the precursor form of IL-1 α , and not IL-1 β , was identified as the predominant IL-1 molecule released by hypoxic keratinocytes. IL-1 α was essential to the initial leukocyte infiltration, but IL-1 β was pivotal to sustaining leukocyte infiltration at later time points. The early IL-1 α -driven phase of inflammation correlated with neutrophil infiltration, whereas macrophages dominated infiltrates measured during the latter IL-1 β -driven phase. Overall, these results identify unique roles for IL-1 α and IL-1 β during hypoxia-triggered inflammation, providing insight into the development of novel therapeutics for the treatment of tissue injury.



Abundant Ag Exhausts Response

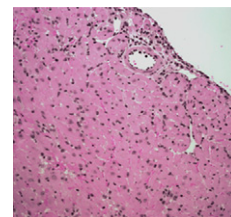
Multiple factors contribute to the suboptimal responses of T cells to tumors following variant peptide vaccination. Kemmler et al. (p. 4431) examined how elevated expression of GP70, a tumor Ag expressed by endogenous murine leukemia virus, alters T cell responses to the tumor-associated Ag AH1 (GP70₄₂₃₋₄₃₁). Young and aging mice were immunized with two different AH1 variants. Variant A5 differs by 1 aa from AH1, and variant 39 differs from AH1 at 6 of 9 aa. Variant A5 induced potent crossreactive T cell responses to AH1 in young but not aging mice, and the reduced variant A5 response in aging mice was associated with increased GP70 expression. Variant 39 immunization elicited T cells in young and aging mice, but these T cells were not responsive to ex vivo stimulation with AH1 peptide. Wild-type AH1 immunization induced tolerogenic responses such that AH1-crossreactive CD8⁺ T cells were suppressed upon subsequent immunization with variant A5 or 39. Interestingly, A5-specific CD8⁺ T cells from naive mice expressing high levels of GP70 also expressed PD-1 and had reduced expression of IL-7R α , which may be due to anergy or exhaustion of this subset. These observations provide a new perspective of the influence that endogenous tumor Ag expression has on variant peptide vaccination, which may improve development of therapeutic cancer vaccines.

IRF7 TRIMs Down

Type I IFN responses are pivotal to innate antiviral immunity, and IFN regulatory factor 7 (IRF7) is a key transcription factor involved in regulating type I IFN expression. IRF7 can be negatively regulated by modification with small ubiquitin-related modifiers (SUMOs). Liang et al. (p. 4754) now show that SUMOylation of IRF7 is promoted by its interaction with tripartite motif-containing protein 28 (TRIM28). TRIM28 has been defined as a transcriptional corepressor of several transcription factors and has SUMO E3 ligase activity. In this study, immunoprecipitation analysis demonstrated that TRIM28 binds directly to IRF7. SUMOylation of IRF7 increased through its direct interaction with TRIM28, and the SUMO E2 enzyme also interacted with TRIM28, thus confirming that TRIM28 functions as a SUMO E3 ligase of IRF7. Viral infection or overexpression of TRIM28 increased SUMOylation of IRF7 and inhibited type I IFN responses. In contrast, knockdown of TRIM28 expression by small interfering RNA reduced IRF7 SUMOylation and did not limit type I IFN antiviral responses. Overall, these findings provide new insight into regulation of type I IFN responses through modulation of IRF7 activity by TRIM28-mediated SUMOylation.

IL-33 Enlists Tolerance Troops

IL-33 is a cytokine known to stimulate proinflammatory Th2 responses, but it has also been shown to have cardioprotective effects. Turnquist et al. (p. 4598) now report that IL-33 promotes cardiac allograft survival in mice by inducing expansion of a variety of immunoregulatory cell subsets. CD11b⁺ myeloid-derived suppressor cells (MDSCs) with intermediate expression levels of Gr-1 expanded in mice treated with IL-33 and strongly suppressed T cell responses relative to cells from control-treated mice. IL-33 also stimulated expansion of CD4⁺Foxp3⁺ T cells with suppressive activity, and this T cell subset originated from natural regulatory T cells (Tregs). ST2L, a membrane-bound molecule that forms part of the IL-33R, was expressed by a large fraction of CD4⁺Foxp3⁺ T cells. Both soluble ST2 and ST2L were upregulated in rejected cardiac allografts, but IL-33 treatment prolonged graft survival by promoting ST2 expression in recipients. IL-33 promoted infiltration of CD4⁺Foxp3⁺ Tregs and CD11b⁺Gr-1^{int} MDSCs into cardiac allografts, and Ab depletion studies confirmed that the Tregs were essential to allograft survival. These findings broaden our understanding of the pleiotropic effects of IL-33 on immune tolerance and graft survival and suggest that IL-33 may have therapeutic applications in transplantation.



Summaries written by Christiana N. Fogg, Ph.D.