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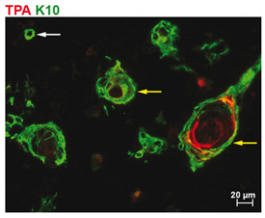
Tracing mTECs with TPA

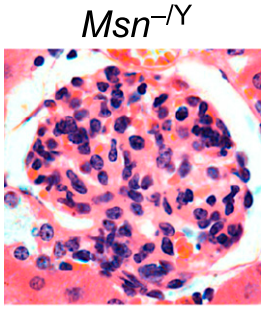


Medullary thymic epithelial cells (mTECs) are known to play a key role in T cell central tolerance. Recent lineage tracking studies have extended the two-step terminal differentiation model of mTEC development from immature MHC class II (MHCII)^{lo} to MHCII^{hi} mTECs to include a third, post–autoimmune regulator (post-Aire) MHCII^{lo} stage. In an effort to further characterize the road map of mTEC differentiation, Michel et al. (p. 3488) demonstrate in this issue that the lectin *Tetragonolobus purpureas* agglutinin (TPA) may be used to discriminate MHCII^{lo} post-Aire mTEC stages that are phenotypically indistinguishable using bona fide terminal differentiation markers such as involucrin (Ivl) and keratin 10 (K10). Staining of murine thymic cells for TPA demonstrated that TPA-positive cells were exclusively localized to the thymic medulla. Costaining for TPA and MHCII further allowed division of MHCII^{lo} and MHCII^{hi} mTECs into TPA^{hi} and TPA^{lo} subsets and the authors found that the TPA^{hi} populations expressed significantly elevated levels of terminal differentiation markers Ivl and K10. Correlation of *Ivl* and *K10* mRNA expression profiles of mTEC subpopulations with surface TPA staining allowed the authors to delineate the following mTEC developmental sequence: TPA^{lo}MHCII^{lo} → TPA^{lo}MHCII^{hi} → TPA^{hi} MHCII^{hi} → TPA^{hi}MHCII^{lo}. This sequence was further validated in vivo by TPA staining of mTECs in an Aire lineage tracing model and was also observed during embryonic development. Further analysis of these subsets demonstrated that the MHCII^{hi} mTECs were highly proliferative, irrespective of Aire or TPA positivity, a phenotype consistent with an intermediate phenotype. MHCII^{lo} mTECs were found to be more prone to apoptosis, with the highest level of expression of annexin V observed among pre-Aire TPA^{lo}MHCII^{lo} mTECs. Furthermore, the expression of FoxN1, a transcription factor implicated in TEC terminal differentiation, inversely correlated with the rate of apoptosis in all mTEC subsets, indicating a prosurvival role for FoxN1 mTEC development. Finally, the authors confirmed that TPA also subdivided human mTECs into four developmental stages. Taken together, this study demonstrates that TPA may be used to delineate stages of mTEC development, revealing a previously unrecognized apoptotic-prone step that may be used for "quality control." These newly dissected stages show parallels between mTEC development and that of cornification of keratinocytes in the upper layer of the skin.

Making Sense of Macaque MHC I

Macaques are used to model human infections, particularly HIV, as they share many similarities with humans in how their immune systems respond to pathogens. MHC class I (MHC I) molecules in macaques share structural and functional similarities with human MHC I, and *Mamu-A1* (*A1*) is an MHC I gene that encodes a molecule with classical peptide presentation function similar to that of HLA-A and HLA-B in humans. In contrast, little is known about *Mamu-A2*05* (*A2*05*) a gene of great abundance in some macaque species. Comparative analysis of *A1* and *A2*05* genes from cynomolgus, pigtailed, and rhesus macaques revealed a greater level of sequence conservation in *A2*05* alleles across these species compared with *A1*, especially in those sequences encoding the B and F peptide binding pockets. Mamu-A2*05:01 preferentially bound 8-mer peptides, and also showed preferential binding to peptides with basic amino acids at p2 and polar and hydrophobic C-terminal amino acids, a property shared with HLA-B*27 and Mamu-B*008:01. Previous work has shown that Mamu-A2*05 has low cell surface expression, and de Groot et al. (p. 3679) observed increased intracellular retention of this molecule within the endoplasmic reticulum. Additional in vitro analysis confirmed that Mamu-A2*05:01 can bind CTL epitopes of viral origin, suggesting that this MHC molecule is transported to the cell surface only when it binds an appropriate peptide. Together these results characterize the unique properties of the macaque *A2*05* gene and how this impacts the specialized Ag presentation by Mamu-A2*05.

Moesin Modulates Homeostasis



Moesin is a member of the ezrin–radixin–moesin (ERM) protein family that links actin filaments with plasma membrane proteins and is expressed in all cells of hematopoietic origin. Recent studies in both humans and mice have linked moesin mutations or deficiency to dysregulation of lymphocyte homeostasis. Satooka et al. (p. 3418) used moesin-deficient ($Msn^{-/Y}$) mice to better understand the immune mechanisms behind this observation. Whereas young $Msn^{-/Y}$ mice appeared generally healthy, aged $Msn^{-/Y}$ mice were more lethargic and had a higher mortality rate than control $Msn^{+/Y}$ mice. Aged $Msn^{-/Y}$ mice also had significantly higher titers of anti-dsDNA Abs and evidence of C3 and IgG deposition in the kidneys, thus manifesting a systemic lupus erythematosus–like autoimmune disease. Analysis of different lymphocyte subsets revealed an expansion of germinal center B cells and accumulation of follicular helper T cells in the spleens of young $Msn^{-/Y}$ mice, which could contribute to anti-dsDNA Ab production. Compared to control mice, young $Msn^{-/Y}$ mice also had a significantly lower

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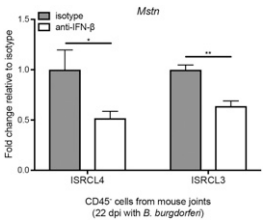
number and proportion of splenic $CD8^+CD44^+CD122^+$ $Ly49^+$ regulatory T (Treg) cells, and this was associated with decreased IL-15–driven $CD8^+$ Treg proliferation. Together these results indicate that moesin is critical to $CD8^+$ Treg homeostasis through cell-intrinsic mechanisms that modulate IL-15 signaling, and suggest that moesin deficiency can thereby have a profound effect on autoimmune disease and mortality.

Myostatin and Lyme Arthritis



Borrelia burgdorferi infection can lead to chronic conditions including Lyme arthritis, but C57BL/6 (B6) mice typically develop mild arthritis, whereas C3H mice develop more severe arthritis. Forward genetic analysis linked the *Bbaa1* locus, which contains the type I IFN gene cluster, to these different manifestations. Human Lyme disease is also associated with a type I IFN signature, and Paquette et al. (p. 3525) used B6 mice carrying the locus from C3H mice (B6.C3-*Bbaa1*) to identify the components of type I IFN signaling that contribute to Lyme arthritis. Ab blockade of IFN-β, but not IFN-α, production in *B. burgdorferi*–infected B6.C3-*Bbaa1* mice was associated with reduced arthritis symptoms relative to treatment with isotype controls. Treatment of *B. burgdorferi*–stimulated bone marrow–derived macrophages with anti–IFN-β, but not anti–IFN-α, suppressed IFN-inducible gene expression. Using reciprocal radiation chimeras in which lethally irradiated B6 or B6.C3-*Bbaa1* mice were reconstituted with autologous bone marrow or bone marrow from the heterologous strain confirmed that both radiation-resistant and radiation-sensitive hematopoietic lineages contribute to Lyme arthritis. The authors defined the congenic interval within *Bbaa1* exerting the most impact on the IFN response using interval-specific recombinant congenic line 3 (ISRCL3) and ISRCL4. RNA sequencing analysis of $CD45^-$ joint cells from chronically infected mice carrying ISRCL3 or ISRCL4 showed that myostatin was unexpectedly associated with IFN-β production, and that arthritis was suppressed in these mice by inhibition of myostatin during infection. Together these results indicate that myostatin contributes to Lyme arthritis by influencing type I IFN responses.