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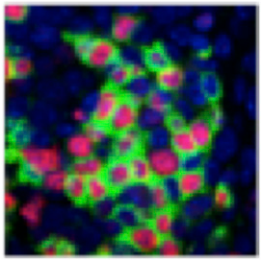
Prime-Pull-Amplify To Protect from STIs

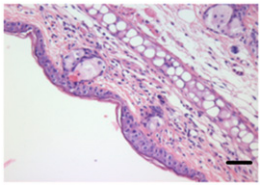


Vaccines for sexually transmitted infections are dependent on induction of both systemic and tissue-resident memory (T_{RM}) Ag-specific $CD8^+$ T cells. In this issue, Çuburu et al. (p. 1250) assessed strategies to maximize circulating and intraepithelial genital $CD8^+$ T cells directed against human papillomavirus (HPV). Using a heterologous prime-boost immunization regimen with nonreplicating viral vectors, the authors demonstrated that i.m. priming followed by an intravaginal (Ivag) boost strongly induced both systemic and genital tract memory $CD8^+$ T cell responses. Furthermore, Ivag boosting with vectors that express vaccine Ags was found to be superior at recruiting and increasing the pool of cervicovaginal $CD8^+$ T_{RM} cells. Transient Ag expression by cervicovaginal keratinocytes also increased trafficking of cognate circulating activated $CD8^+$ T cells and induced proliferation and differentiation of Ag-specific $CD8^+$ T_{RM} cells. The authors also showed that induction of secondary $CD8^+$ T_{RM} cells was independent of $CD4^+$ T cell help during Ivag booster immunization. Importantly, this prime-pull-amplify vaccination strategy induced systemic and local $CD8^+$ T cell responses against high-risk HPV type 16 E7 oncoprotein and conferred protection against a genital vaccinia challenge. Together, these results highlight the importance of delivery routes for nonreplicating viral vectors in prime-boost immunization strategies and demonstrate that Ag expression at the site of entry can guide $CD8^+$ T cells to where they are needed most. Such an approach may be used to improve vaccinations against sexually transmitted infections.

Utx Regulation of T Cell Memory

Histone H3K27 methylation influences stem cell differentiation, and trimethylation of this histone residue (H3K27me3) is highest in naive and central memory compared with effector memory cells. Utx is a histone H3K27 demethylase that has been shown to regulate differentiation of T follicular helper cells, but its role in $CD8^+$ T cell differentiation is not as well understood. In this issue, Yamada et al. (p. 1088) use *Utx* KO mice to understand its function in Ag-specific $CD8^+$ T cells. *Utx* KO mice infected with *Listeria monocytogenes* expressing OVA (Lm-OVA) had more OVA-specific $CD8^+$ T cells compared with WT mice after challenge. Through a cell-intrinsic mechanism, memory $CD8^+$ T cells were significantly higher in number in *Utx* KO mice, and this was associated with greater memory precursor formation due to decreased demethylation of H3K27me3 in the *Prdm1* gene locus. $CD8^+$ T cells treated with Utx cofactor α-ketoglutarate showed decreased memory formation, whereas treatment with GSK-J4, a Utx inhibitor, was associated with greater memory T cell formation. Together, these results uncover new epigenetic mechanisms whereby Utx negatively regulates memory $CD8^+$ T cell formation.

Cathepsin G and Hypersensitivity



Contact hypersensitivity (CHS) is an inflammatory response mediated by hapten-reactive T cells. Previous studies have shown that Gr-$1^+$$CXCR2^+$ granulocytes are recruited to hapten-challenged skin by CXCL1/CXCL2 and are required for hapten-specific $CD8^+$ T cell–mediated CHS. In this issue, Kish et al. (p. 1045) find that $CD4^+$ T cell–mediated CHS can occur in CXCR2-deficient mice as well as in WT mice that undergo neutrophil depletion during hapten sensitization with 2,4-dinitrofluorobenzene. Hapten-reactive $CD4^+$ T cells require IL-12 during sensitization to become IFN-γ–producing cells that mediate CHS, and these cells can be primed to promote CHS in cathepsin $G^{-/-}$ mice. These observations suggest that the absence of neutrophil capthepsin G allows for IL-12 production and primes hapten-specific $CD4^+$ T cells to produce IFN-γ rather than IL-4/IL-10, which is observed in the presence of neutrophils. Together, these findings reveal a role for neutrophil cathepsin G in regulating $CD4^+$ T cell–mediated CHS.

A Role for Ikaros in Mature T Cells

Ikaros is a transcription factor widely expressed in hematopoietic cells and is critical for T cell development in the thymus. Lyon de Ana et al. (p. 1112) examine the function of Ikaros specifically in mature $CD4^+$ T cells using an Ikaros conditional knockout mouse (Ik^{flox}). $CD4^+$ T cells from these mice differentiated into Th1, Th2, and Th17 lineages but not into inducible regulatory T cells (iTregs). Gene expression analysis indicated that Ik^{flox} mice had a shift toward genes associated with inflammatory cytokines. In addition, the absence of Ikaros in $CD4^+$ T cells was associated with dysregulation of type I IFN genes. These findings indicate that Ikaros plays a critical role in regulating cytokine expression in mature $CD4^+$ T cells, which may be crucial to curbing inflammation and autoimmunity.

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