The androgen receptor tunes CD8$^+$ T cell effector and memory responses to acute infection

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Cancer immunotherapies are FDA approved in over 50% of advanced and/or metastatic cancer patients. Despite their widespread use, response rates have plateaued at approximately 20%. Our group has leveraged the impenetrable nature of prostate cancer to immunotherapy to decipher novel mechanisms of immunotherapy resistance. In this regard, we have described a role for the androgen receptor (AR) in limiting CD8 T cell anti-tumor activity by inhibiting IFNγ production and response to immune checkpoint blockade. However, the mechanisms by which AR regulates CD8 T cell differentiation and function are unknown. Thus, we have defined the AR regulatory network in T cells and revealed AR-mediated epigenetic and transcriptional regulation of effector- and memory-associated genes. AR protein interactions with epigenetic regulators from the BAF complex and histone deacetylases were identified, underscoring epigenetic remodeling enforced by androgens. In mouse models of infection, we demonstrate that genetic deletion of *Ar* in CD8 T cells enhances the effector response by increasing proliferation, function, and effector differentiation. Furthermore, deletion of *Ar* in CD8 T cells skews effector memory differentiation and improves recall protection. Interestingly, AR expression rapidly increases in CD8 T cells during priming, which is associated with AR-induced changes in chromatin accessibility. Importantly, the observations made in AR-deficient CD8 T cells are phenocopied in female CD8 T cells when compared to males. These data suggest that AR regulates epigenetic and transcriptional changes induced during T cell activation and differentiation, thereby tuning CD8 T cell effector and memory responses and contributing to sex differences in adaptive immunity.