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Androgen Receptor Regulation of T Cell Immune Responses

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Abstract

Sex differences in disease susceptibility, including infection, cancer, and autoimmunity, have been well-characterized, with males generally being more susceptible to infections and malignancies, and females more susceptible to autoimmune diseases. While many factors underlie such differences, sex differences in T lymphocytes differentiation and function likely lead to disparate adaptive immune responses and disease control. Indeed, sex hormones, including androgens, are strong regulators of gene expression, and have been implicated as drivers of immunity and regulators of T cell differentiation. Therefore, it is clear that androgens play a role in the regulation of T cell function and differentiation, but the mechanisms of such control remain unknown, including whether such regulation is cell-intrinsic. Our findings reveal that androgen receptor (AR) activity suppresses T cell activation and leads to a reduction in T cell proliferation and effector function. We show via flow cytometry that mouse cytotoxic T cells from *in vitro* peptide-stimulated splenocytes exhibit enhanced proliferation and effector cytokine production, and reduced epigenetic inhibitory histone modifications in response to AR inhibition. Further, we demonstrate ligand-dependent binding of AR to genetic loci of effector and differentiation genes in mouse cytotoxic T cells via chromatin immunoprecipitation and quantitative PCR. Finally, *in vivo* murine models of lymphocytic choriomeningitis virus (LCMV) reveal an increase in AR mRNA expression in virus-specific cytotoxic T cells following infection, which persists in memory T cells after resolution of infection. Altogether, these data suggest that AR regulates epigenetic and transcriptional changes induced during T cell activation and differentiation, thereby dampening the T cell response. These findings further suggest that targeted disruption of AR activity in T cells may be a viable therapeutic approach for altering the T cell response in the context of human diseases.