Guardians of Sperm: How Epithelial and Immune Cells in the Epididymis Shape Male Fertility

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Nearly half of male infertility cases are “idiopathic,” reflecting major gaps in our understanding of male reproductive tract function. Immune factors may account for up to 15% of cases, though this is likely underestimated due to limited characterization of the epididymal mucosa. The epididymis represents one of the most intriguing immune environments in the body, where tolerance to highly antigenic sperm must coexist with the capacity to mount rapid and effective responses against pathogens. Understanding how this balance is achieved is fundamental to male reproductive health and fertility.

Our laboratory has uncovered previously unrecognized mechanisms by which epithelial proton-secreting clear cells orchestrate immune homeostasis and sperm maturation within the epididymis. Beyond their established role in luminal acidification, we demonstrate that clear cells actively communicate with region-specific mononuclear phagocyte populations to regulate the balance between immune tolerance and inflammation. We further identified novel functions for clear cells in sperm maturation, including the transfer of previously unrecognized proteins to developing sperm through extracellular vesicles and nanotubular structures during epididymal transit.

Using complementary models of infectious and autoimmune inflammation, we have defined the immune landscape of the epididymis under physiological and pathological conditions. Our studies characterize the phenotypic diversity, morphology, and antigen-handling properties of region-specific mononuclear phagocytes and reveal complex, region-dependent communication networks between epithelial and immune cells. During lipopolysaccharide-induced epididymitis, these interactions drive distinct innate and adaptive immune responses that compromise epithelial integrity and impair fertility. In a model of autoimmune epididymitis induced by regulatory T-cell depletion, we discovered the formation of tertiary lymphoid structures within the distal epididymis that function as local sites of autoantibody production and chronic inflammation, providing a mechanistic link between loss of immune tolerance and male infertility.

Together, these findings redefine the epididymis as a dynamic mucosal immune organ in which epithelial and immune cell crosstalk is essential for maintaining reproductive homeostasis. This work advances our understanding of mucosal immunity in the male reproductive tract and identifies new cellular and molecular pathways that may serve as therapeutic targets for inflammatory male infertility and the development of non-hormonal male contraceptive strategies.