RESEARCH HIGHLIGHT

ILC2s govern sex-differential immunity in skin

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The mechanisms driving sex differences in immunity are poorly understood and likely vary by body site; thus Chi et al. investigated the mechanistic basis of sex differences in tissue-specific immunity in a recent paper in *Science*. They focused on the complex network of immune cells in murine skin to demonstrate that an androgen-ILC2-dendritic cell axis drives sex differences in immune homeostasis in the skin that is modulated by sex-differential microbiota.

Sex differences in innate and adaptive immunity, susceptibility to multiple diseases and responses to therapeutic interventions are widely described,[1] yet the mechanisms remain mostly elusive. The two dominant factors thought to drive immunological sex differences are sex hormones and sex-linked immune response genes, mostly X-chromosome linked.[1] The microbiome also differs in males and females due to bi-directional interactions between the immune system, sex hormones and microbial communities, leading to the concept of the microgenderome,[2] which further contributes to sex-differential immunity.

Chi et al.[3] investigated the mechanisms of sex differences in tissue-specific immunity in mice and identified the skin as a key organ exhibiting marked sex differences in immune cell composition, with females having greater numbers of type 1 (Th1, Tc1), type 17 (Th17, Tc17) and regulatory T cell (Treg) subsets. Differences were apparent in germ-free mice confirming that they were not driven by sex-differential microbiota, while introducing microbiota-augmented type 17 and Treg responses in females. The authors went on to demonstrate that females have more robust immunity to skin commensals and invading bacterial pathogens than males. Females had greater Tc1 and IL-17A expressing T cell subsets in response to colonization with *Staphylococcus epidermidis*, *Corynebacterium accolens* and *Candida albicans* which in turn led to enhanced immune responses in keratinocytes and lower bacterial load among females. The immune response to skin infection with *Staphylococcus aureus* similarly resulted in greater Th1 and Th17 immunity in females compared to males. Pre-pubertal male castration led to a loss of the above sex differences, whereas ovariectomy had no effect, suggesting that male sex hormones drive the lymphoid sex differences and response to microbiota.

Within the skin dendritic cell (DC) network, females had greater DC numbers which expressed more co-stimulatory and survival genes and had greater migratory and antigen presenting capacity, whereas male DCs expressed more negative regulatory genes. Castration and hormone treatment experiments demonstrated that male sex hormones negatively regulate skin DC homeostasis and function. Since skin DCs do not express the androgen receptor (AR), an intermediary AR-expressing population was sought. The authors identified type 2 innate lymphoid cells (ILC2s) as the AR-expressing population required for skin DC homeostasis. Indeed, absence of ILC2s led to a profound disruption of the DC network and loss of the DC sex bias which could be mostly restored by adoptive transfer of ILC2. They further demonstrated that GM-CSF produced by ILC2s stimulates the local accumulation of skin DC. The negative regulation of ILC2s by androgens causes a lower accumulation and activation of skin DC in males compared to females, an effect further calibrated by the skin microbiota. Therefore, male sex hormones drive the differences in mouse skin immunity via what the authors termed the androgen-ILC2-DC axis, a novel immunoregulatory pathway, possibly unique to skin.

It is often assumed that sex hormones play an antagonistic role with heightened immunity in females driven by estrogen and suppressed immunity in males due to the immunosuppressive effects of androgens.[1] However, this study points to a role of testosterone alone in driving immunological sex differences in the skin. The net effect is a better barrier function in female mice compared to their male counterparts, with type 1 (IFN-γ) and type 17 (IL-17) responses specifically upregulated in female skin as compared to males.

The relevance of the author's findings to humans is not known but one would speculate that they contribute to sex differences in various skin conditions, and if so, hormone treatment, immunotherapy and microbiota manipulation might hold the key to treatment. In general, females suffer more frequent skin and skin-related diseases than males. For example, females have a greater tendency to develop cutaneous manifestations of connective tissue diseases such as scleroderma, dermatomyositis, Sjögrens syndrome, systemic lupus erythematosus and hidradenitis suppurativa, perhaps due in part to heightened type 1 and type 17 inflammatory responses, although males suffer more psoriasis and psoriatic arthropathy.[4] Interestingly, anti-IL-17 therapy is a licensed treatment for hidradenitis suppurativa and psoriasis indicating a key role for type 17 immunity in mediating these conditions.[5] Males suffer more frequent cutaneous basal cell carcinoma (except in females ≤ 40 years) and squamous cell carcinoma,[4] and greater male progression and mortality from melanoma has been linked with testosterone levels and activity.[6]

The author's findings of sex-differential responses to *S. aureus* infection are of considerable interest since it is the most common cause of skin and soft tissue infection (SSTI) and the leading bacterial cause of global mortality.[7] Males have more than double the risk of developing *S. aureus* SSTI and increased risk of invasive infection,[8] which fits the findings of greater Th1 and Th17

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immunity in female skin in response to *S. aureus* infection. While Castleman et al.[8] described an estrogen-dependent mechanism for sex differences in *S. aureus* infections, it would be worth exploring whether the androgen-ILC2-DC pathway also plays a role. The skin is a therapeutic target for topical drug applications and intradermal and subcutaneous injections, including vaccines. One would predict that the findings described in this paper would result in greater immune responses among females to skin-directed treatments compared to males. Indeed, local skin reactogenicity to vaccination is generally greater among females than males, as are responses to intradermally and subcutaneously administered vaccines such as BCG, smallpox and Q-fever vaccines.[9]

We are still a long way from understanding the mechanisms of the many described sex differences in diseases. The role that the novel androgen-ILC2-DC pathway plays in controlling sex-differential immunity and disease susceptibility in humans should be explored and may reveal novel treatment strategies for the plethora of skin conditions which manifest differently in males and females.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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