Why Sex Matters for Women

Sex is complicated for many reasons, but *especially* when the immune system is involved.

Classification of biological sex in 98% of the population is easy: you're either male or female, depending on your chromosomes, hormones, and reproductive system. For women, however, the immune system can be a double-edged sword; on one hand, it protects, but on the other hand it *tortures* them with autoimmunity. The only autoimmune diseases which affect men more than women are Primary Sclerosing Cholangitis (PSC), Ankylosing Spondylitis, and Type 1 Diabetes Mellitus. Even then, the severity of these diseases is still worse in women (barring PSC).

It seems that the female immune system may be protecting us from the outside, but it also turns against us at the worst possible times. So, is the patriarchy really ingrained into our DNA? *To answer this question, keep reading!*

Hormones & The Reproductive System

The last two years of research have shone a spotlight on the female immune system's fixation with torture. In 2025, a study containing almost 3,5 million patients showed that women taking the combined oral contraceptive (oestrogen and progesterone) showed a higher incidence of multiple different immune-mediated diseases compared to those taking the progesterone-only contraceptive pill. Furthermore, blocking oestrogen's effects in the body has been considered to treat certain autoimmune conditions, including Autoimmune Hepatitis.

Unfortunately, less oestrogen isn't helpful, as shown in those who are menopausal. Early onset-menopause is associated with the development of Rheumatoid Arthritis and increased severity of the disease. The reproductive system is both a blessing and a curse in terms of sex, although its role in the immune system is far less overt.

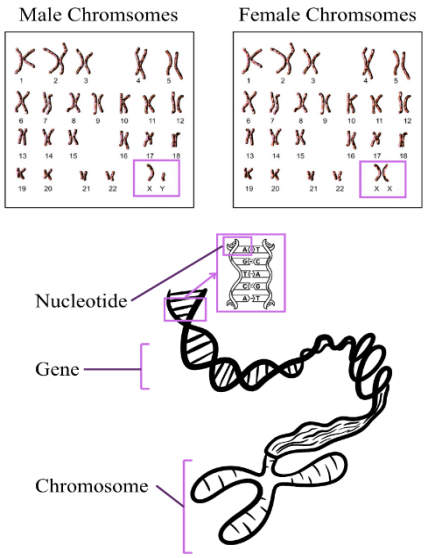

Figure 1: Human Karyotype with autosomes (non-sex chromosomes) and sex chromosomes indicated. DNA structure is pictured.

Chromosomes & Genes

The X chromosome (see *Figure 1*) carries many immune-related genes, including those involved in cell differentiation and function. Of course, differences in functionality arise because men have one X and women have two X chromosomes. Within these genes themselves, differences of a single nucleotide (a single nucleotide polymorphism, or SNP) can affect a person's risk for autoimmune disease development, such as in the case of the *TLR7* gene, affecting susceptibility to Systemic Lupus Erythematosus development in women. *TLR7* codes for a gene that helps the body distinguish its own tissue and invading bugs and subsequently a faulty gene blurs the boundary between self and non-self.

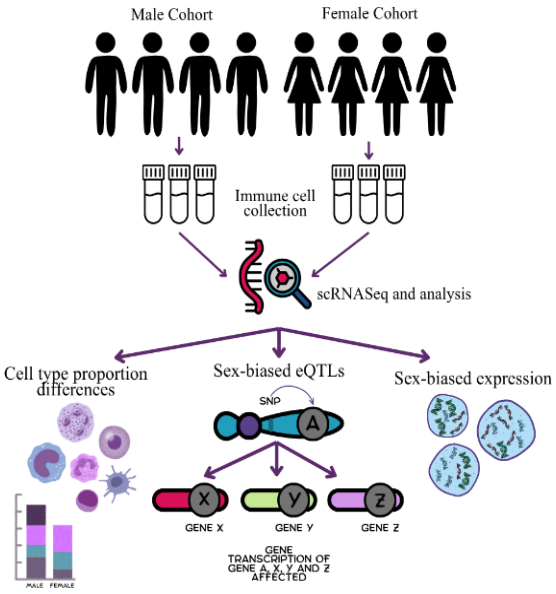

Figure 2: Methods of the study

The Tasmanian Study

The researchers in a 2026 Tasmanian study set out to answer how genetic variation and differences in expression at a cellular level can drive sex-bias in the immune system. They performed single-cell RNA sequencing to examine roughly 1,2 million immune cells from nearly 1000 people. They then compared the proportions of these immune cells between men and women, and identified genes with higher expression levels in one sex than the other. To help investigate *why* these genes were expressed differently, they looked at eQTLs (DNA variants which help regulate the degree of gene expression).

So what did they find?

They found differences in immune cell proportions. Interestingly, on average, women had higher ratios of B cells, which produce antibodies, and T regulatory cells (Tregs), which are ordinarily responsible for suppressing inflammation. The Tregs bit may seem contradictory, as more regulation *should* reduce autoimmunity. Oestrogen can increase Tregs, but that does *not* mean that they're working. On top of that, this apparent protective effect may be outweighed by the pro-inflammatory gene activation women show.

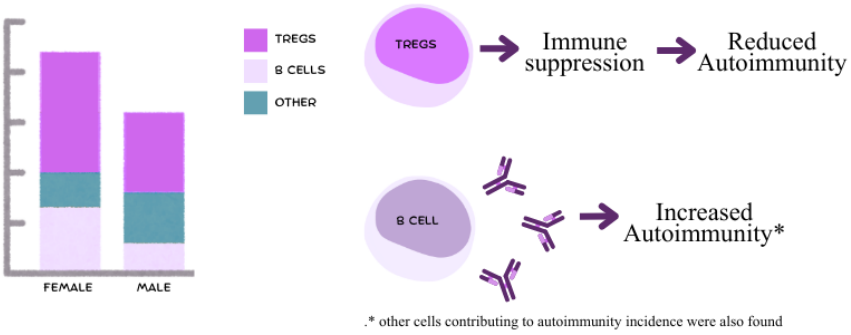

Figure 3: Simplified cell proportion results

Now, onto the genes. Naturally, they found differences in X-linked genes between men and women (*Figure 1*). However, most of the variations in gene expression were actually found in autosomal chromosomes. *Weird, right*? Overall, women had greater enrichment of inflammatory pathways, such as TNFα-signalling and IFNγ-signalling, both of which are pro-inflammatory molecules. These may then contribute to women's increased autoimmune activity. Men on the other hand had alterations in RNA metabolism, protein translation, and ribosomal function, which may contribute to their altered susceptibility to non-reproductive-system cancer. To further analyse *why* these genes may be so variably expressed, they looked at eQTLs and found many male- and female-specific variations, but these variations were limited on the X chromosomes. Hence, a lot of the immune regulation seems to arise from autosomal chromosomes, rather than on the basis of sex!

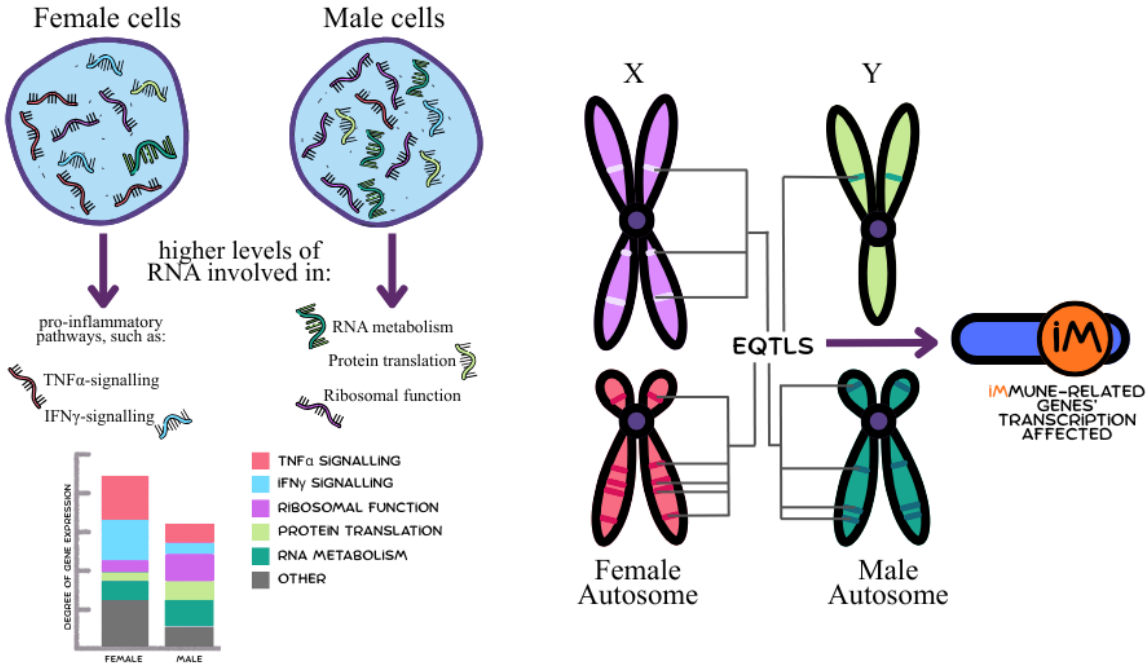

Figure 4: Simplified RNA expression levels and eQTLs

So, is the immune system seXXist? Perhaps not. Although women struggle more with autoimmunity, this heightened inflammation may protect from infection. Understanding these biological differences matters, because it brings us closer to developing personalised medicine for patients. However, only time will tell if science can discover why women never fall ill to the dreaded *man-flu*.

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