UCL Press Release

Abundance of key immune cells may be influenced by oestrogen and XX chromosomes

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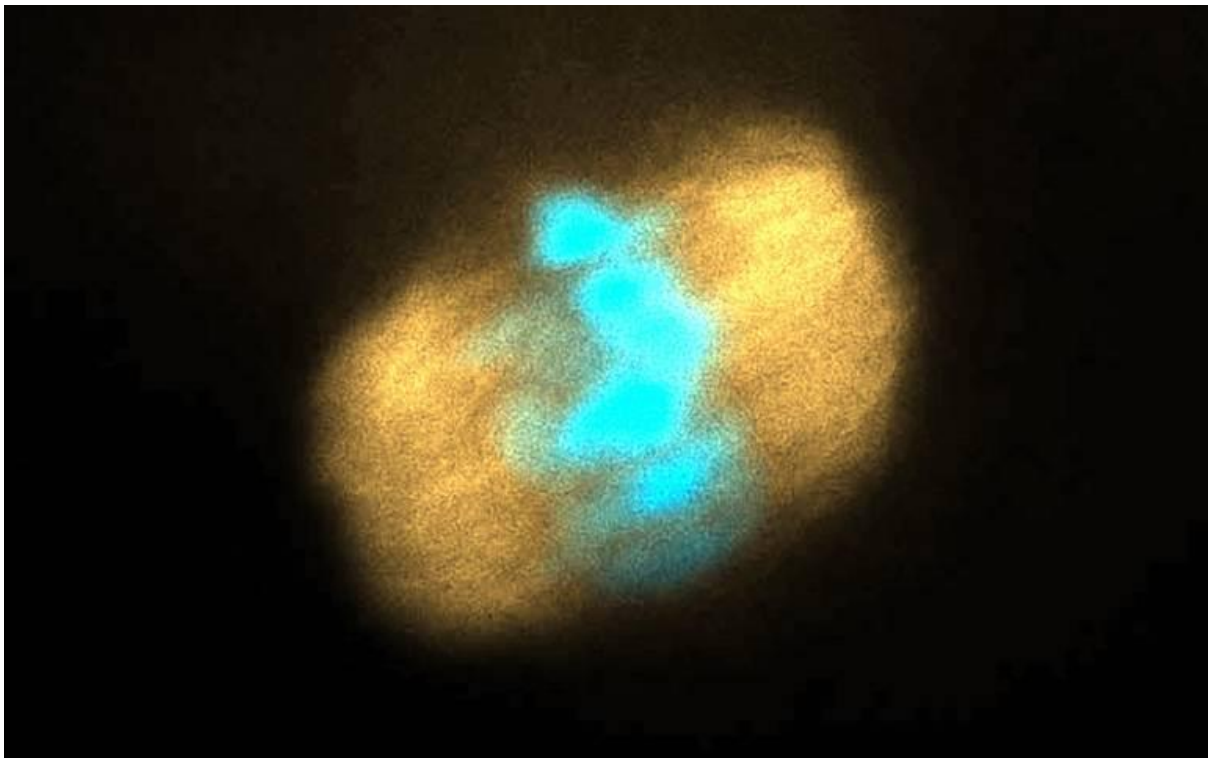
Women have a higher proportion of key immune cells between puberty and menopause, which may be linked to the sex hormone oestrogen and explain why they are less susceptible to certain infectious diseases than men, according to a new study led by researchers at UCL.



The study, published in the *Journal of Experimental Medicine*, is one of the first to explore how sex chromosomes and sex hormones combine to influence the immune systems of healthy individuals across a wide range of ages and gender profiles[1].

Explaining the importance of the paper, Dr Elizabeth Rosser, a senior author of the study from UCL Division of Medicine and at the Centre for Adolescent Rheumatology at UCL, said: “Sex and gender are frequently overlooked in medical research, despite evidence that many females typically produce ‘stronger’ immune responses to infections such as COVID-19 than males, while also having a greater risk of developing autoimmune conditions such as lupus and rheumatoid arthritis.

“The primary sex hormones – oestrogen in females and testosterone in males – are thought to play a role in these differences, as are the sex chromosomes (XX in people registered female at birth, and XY in people registered male at birth).

“However, very little is known about how immune health outcomes may change during puberty or menopause, or for transgender individuals in receipt of gender-affirming or puberty suppressing hormone treatments.”

In order to examine how hormones and biological sex influence the production of 31 different immune cell types, the team analysed blood samples from 283 individuals between the ages of six and 84 years.

Of these, 203 were cisgender[1] females and cisgender males, including post-menopausal women receiving hormone replacement therapy (HRT). They also analysed samples from 80 transgender[1] females and males receiving gender-affirming or puberty suppressing hormone treatments[2].

The results indicated that cisgender females (XX chromosomal background) have higher levels of specific white blood cells, known as class-switched memory B cells, than cisgender males (XY chromosomal background).

Class-switched memory B cells, which are a major component of the immune system, have undergone a process known as 'class-switching' that makes them highly efficient at fighting infections that the body has encountered before. But these 'specially trained' B cells may also lead to more severe symptoms if the person has an autoimmune disorder, where a person's immune system attacks their own healthy tissues.

Crucially, researchers found that these sex differences were only seen between individuals who had completed puberty, but not yet (in the case of cisgender females) gone through the menopause. Along with the fact that B cells have receptors for oestrogen, this finding suggests that oestrogen, which is found at much lower levels in females before puberty and after menopause, may be associated with the increase in class-switched memory B cells.

Professor Coziana Ciurtin, principal investigator of the study from UCL Division of Medicine and the Centre for Adolescent Rheumatology at UCL, said: "Our study has identified some evidence that oestrogen plays an important role in the abundance of class-switched memory B cells in females, but more research is required to fully understand the biological mechanisms at play. However, these findings could partially explain the sex differences we see in many infectious diseases, vaccine responses, and autoimmune disorders, and add to the growing evidence that sex and gender are critical factors to be considered in immunological studies."

The authors say that despite the differences in class-switched memory B cells observed in the different groups, it is not possible to conclude that these differences are 'good' or 'bad' in terms of overall health. While cisgender females do have better protection against infectious diseases such as COVID-19 and hepatitis B, this is balanced out by being more susceptible to autoimmune conditions such as lupus. For groups whose B cell populations more closely resemble those in cisgender males, the opposite could be true. Future research would be needed to address this.

The team found that in transgender males (XX chromosomal background) receiving treatment to block their production of oestrogen, levels of class-switched memory B cells were significantly reduced when compared to cisgender females of the same age. These levels were comparable to those seen in cisgender males.

However, when they analysed samples from transgender females (XY chromosomal background) who were taking oestrogen to affirm their gender, their levels of class-switched memory B cells were comparable with those seen in cisgender males.

Professor Lucy Wedderburn from the UCL Great Ormond Street Institute of Child Health and Director of the Centre for Adolescent Rheumatology at UCL, said: "The X chromosome carries numerous genes that are important for human immune responses, so it was critical to find out

whether the effects of oestrogen would be the same in cisgender females and transgender males with two X chromosomes, versus cisgender males and transgender females with only one X chromosome.

“This data from our Centre demonstrates that sex hormones and chromosomes work in tandem to impact immune responses, with oestrogen only influencing the frequency of class-switched memory B cells in individuals with an XX chromosomal background.”

In the samples from cisgender females aged 40-60 years who were receiving HRT, oestrogen was associated with a significant increase in class-switched memory B cells. This further suggests that oestrogen is only associated with this increase in people with two copies of the X chromosome.

The authors say that the research highlights the need for further high-quality, long-term studies to examine the impact of hormonal treatment on infection and autoimmunity risk across a range of sex chromosomal backgrounds and stages of life.

Dr Hannah Peckham, first author of the study from UCL Division of Medicine, UCL Great Ormond Street Institute of Child Health, and the Centre for Adolescent Rheumatology at UCL, said. “Our study demonstrates that improvements in diversity and inclusion practices within medical research will not only advance our scientific understanding of sex-biases in disease outcomes, but potentially shed light on novel strategies for personally tailored healthcare and potentially mitigate against health inequalities.”

The study was funded by Versus Arthritis, Great Ormond Street Hospital Children’s Charity, Bart’s Charity, the Medical Research Foundation, NIHR UCLH Biomedical Research Centre and the NIHR Great Ormond Street Biomedical Research Centre.

[1] Cisgender females/women and cisgender males/men are individuals who are registered female or male at birth and still identify as their birth gender. Transgender females/women are individuals who are registered male at birth (XY chromosomes) who identify as female. Transgender males/men are individuals who are registered female (XX chromosomes) at birth who identify as male.

[2]The blood samples taken from the control group of transgender males and transgender females were provided between 2016 to 2020, by the former NHS Gender Identity Development Service. Puberty suppressing hormone treatments (puberty blockers) stopped being prescribed in 2024 in the UK while clinical trials into their efficacy and safety are conducted.

Paper: Estrogen influences class-switched memory B cell frequency only in humans with two X chromosomes - PubMed

Links

- Professor Coziana Ciurtin's academic profile
- Dr Hannah Peckham's academic profile
- Dr Elizabeth Rosser's academic profile
- Professor Lucy Wedderburn's academic profile

- UCL Great Ormond Street Institute of Child Health
- UCL Population Health Sciences
- UCL Division of Medicine
- UCL Faculty of Medical Sciences

Image

- Credit: Meiotic spindle and chromosomes. M. Herbert, A. McDougall & H. Homer. Source: Wellcome Collection.

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