"Scripts" Don't Lie: Sex and Age Shape Blood Immune Gene Expression in Asthma

It has long been recognized that males and females exhibit differences in asthma incidence, severity, and response to treatment throughout the lifespan (1, 2). During childhood, males are more frequently affected than females by asthma, often presenting with heightened type 2 inflammation, increased atopy, and higher serum IgE concentrations (3, 4). After puberty, however, the burden of disease shifts, with females experiencing a higher prevalence, increased exacerbation frequency, and attenuated responses to standard asthma therapies compared with males (1, 5). These differences have been linked to multiple factors in both pediatric and adult populations, including genomic architecture (6, 7) and physiological variations in circulating sex hormone concentrations throughout life (8, 9). In adult women, hormone fluctuations associated with menarche, menstruation, pregnancy, menopause, and the use of hormone therapy have all been linked to changes in asthma symptoms and disease control (3, 9). However, hormonal changes do not fully account for the complexity of sex-specific disease phenotypes observed across the lifespan, suggesting an interaction between genomic, epigenetic, hormonal, and environmental factors (10).

To shed new light on the biological basis of sex differences in asthma, in this issue of the *Journal*, Kay and colleagues (pp. ■■■) present a large-scale transcriptomic meta-analysis of peripheral blood samples (11). Their analysis revealed a distinct pattern of sex-specific immune gene expression in blood samples that was uniquely associated with clinical asthma features such as symptom scores, lung function, and type 2 inflammation. These findings not only advance our understanding of the mechanisms underlying asthma heterogeneity but also emphasize the importance of disaggregating transcriptomic data by sex in research studies.

By using a harmonized analytical pipeline across publicly available datasets, the authors analyzed blood transcriptomic data from 3,639 adult individuals (56% female), comprising both patients with asthma and healthy control subjects. Using this standardized meta-analysis approach improved the statistical power, allowing the detection of subtle yet biologically meaningful sex differences in gene expression. The analysis identified 61 sex-biased genes (SBGs) in blood samples from patients with asthma. Notably, these differences were not found in samples from healthy control subjects, suggesting that these SBGs are either triggered or become more pronounced in the context of the disease. The functional relevance of these SBGs was supported through validation in an independent cohort of 132 adults with asthma (78% female), where their expression patterns were also associated with clinically meaningful asthma traits. Furthermore, the identified SBGs were associated with pathways implicated in lymphocyte activation, innate immune signaling, and adaptive allergic responses, contributing to the growing body of evidence that sex-specific molecular mechanisms underlie the sexual dimorphism observed in asthma pathogenesis (4, 5, 12).

To further explore the tissue specificity of these sex-biased signatures, Kay and colleagues (11) extended their meta-analysis to airway immune and epithelial cell transcriptomes. This analysis revealed that although SBG expression was robustly observed in peripheral blood immune cells, it was much less apparent in airway and epithelial cell samples. This suggests that circulating immune cells may be more sensitive to systemic sex- and age-related factors or that the blood compartment can better capture disease-relevant transcriptional variation in asthma. These findings also underscore the importance of considering the tissue context when interpreting gene expression data (13).

Another notable observation was the age specificity of the identified SBGs. When comparing adult with pediatric transcriptomic data, it was found that the sex-specific gene expression patterns were largely absent in children. This finding suggests that age influences the expression of asthma-related immune genes and supports the existence of a sex-specific inflammatory architecture that manifests as distinct gene expression profiles in peripheral immune cells and evolves with age. This architecture likely reflects the combined effects of sex chromosomes, hormonal regulation, epigenetic modifications, and environmental exposures, contributing to clinically relevant heterogeneity in asthma pathogenesis.

In conclusion, the work presented by Kay and colleagues (11) contributes to our understanding of the transcriptomics-mediated mechanisms that drive sex differences in asthma. The identification of 61 SBGs in peripheral blood samples of adult patients with asthma, together with their association with specific immune cell types, disease clinical features, and type 2 inflammation, provides compelling evidence for a sex- and age-dependent inflammatory landscape, challenging the conventional practice of pooling data across sexes by demonstrating that such aggregation may obscure meaningful biological insights. As the field advances toward precision medicine, incorporating sex- and age-specific transcriptomic insights into research studies will be crucial for better understanding the complexity of asthma and other inflammatory diseases. After all, the immune system's tran"scripts" don't lie. ■

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Patricia Silveyra, Ph.D., A.T.S.F.
Indiana University School of Public Health Bloomington
Bloomington, Indiana

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