MAYO CLINIC

Decoding Sex-Biased Gene Expression Patterns in Heart Disease

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Sex, a biological determinant of a person's anatomy and physiology, has vital implications on disease incidence and prevalence, and ultimately clinical outcome.[1] Recognized across reproductive and nonreproductive organs, distinct phenotypes differentiate women from men not only during the reproductive years but also throughout all of life. Sexually dimorphic expression of sex-linked genes, however, does not account for all sex differences.[2] Rather, the complexity of sex differences in health and disease goes beyond a sex chromosome—directed and hormone-centric axis. Indeed, most autosomal genes with sex-biased expression lack androgen or estrogen response elements.[3] In this context, sex-biased gene expression could engender (patho)phenotypic sex differences whereby autosomal genes, operating identically in males and females to influence a trait, are expressed more or less abundantly in one vs the other sex. An integrative foundation on which to ascertain sex differences is emerging through large-scale data sets, typically sourced from healthy tissues and organs containing multiple cell types. Although a systems-level genetic architecture is thereby increasingly delineated, less is known regarding the recondite sex-segregated differentiators of disease vulnerability.

This issue of *Mayo Clinic Proceedings* features a cell-specific deciphering of gene expression patterns underpinning sex-biased dysregulation in cardiomyopathy.[4] Using patient-derived cardiomyocytes, Gaignebet et al[4] report linkage of an inflammation-related gene signature with poor organ function in males but not in females. In this way, this innovative work ushers in an era of sex-related pathophysiology decoded at a cell-autonomous, molecular level.

Sex in Cardiology

Half of the adult population in the United States—51.2% of men and 44.7% of women—lives with a cardiovascular condition, underscoring the effect on public health.[5] Notably, males and females demonstrate distinct susceptibilities for cardiovascular disorders. For example, premenopausal women, compared with age-matched men, are at reduced risk for coronary heart disease, whereas postmenopausal status is linked with aggravated cardiovascular morbidity and mortality.[6] As life expectancy in men and women is continuously increasingly, with that of women to exceed 90 years of age in this decade, there is an increased emphasis on safeguarding the vulnerable heart. Decoding diverse disease trajectories and cardioprotective patterns naturally occurring in a sex-biased or age-dependent manner would inform a path toward more personalized care.

Sex-Biased Gene Profiling

A contributor to poor prognosis in heart disease is maladaptive myocardial remodeling, known to adopt sex-distinctive features. Males are particularly susceptible and prone to cardiomegaly in the setting of hemodynamic stress. A case in point is advanced left ventricular hypertrophy developing in response to pressure overload imposed by aortic stenosis,[7] a clinical condition studied by Gaignebet et al.[4] Of note, degenerative aortic stenosis in the elderly is the major etiology of nonrheumatic valvular heart disease that accounts for 25,000 deaths annually in this country. Despite a similar extent of outflow obstruction in patients undergoing aortic valve replacement, the left ventricle in males demonstrated structural and functional maladaptation, characterized by an exaggerated increase in chamber size, wall thickness, and mass index and an aggravated decline in contractility. In a sex-biased genomic profile, 2 discrete inflammatory genes, *CCN2* and *NFKB1*, were recognized by high expression in cardiomyocytes obtained from male patients and remarkably correlated negatively

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with ventricular pump function,[4] suggesting a potential molecular mechanism underlying sex-specific disease manifestation.

Linkage to Inflammation and Fibrosis

Tissue inflammation after injury is a physiologic reaction triggering repair but also a promotor for pathologic fibrosis. Due to a limited self-renewal capacity, the human heart is vulnerable to injury and prone to experiencing irreversible damage with cell death, scar formation, mechanical dysfunction, and subsequent organ failure.[8] The 2 identified genes, *NFKB1* and *CCN2*, play critical roles in the cardiac stress response. The *NFKB1* gene encodes the nuclear factor NF-kappa-B p105, a DNA binding subunit of the nuclear factor kappa B (NF-κB). Activated by ischemic and nonischemic challenge, including pressure overload, NF-κB promotes pro-inflammatory gene expression in cardiomyocytes and mediates inflammasome signaling that collectively precipitate a potentially harmful cardiac overreaction by recruiting macrophages, T cells, and fibroblasts.[9] The cellular communication network factor 2 (CCN2), also known as connective tissue growth factor, is a secreted protein that aggravates fibrogenesis and accelerates tissue fibrosis under hemodynamic load.[10] As pro-inflammatory and profibrotic mediators,[9,10] *CCN2* and *NKFB1* may, therefore, working in tandem, expedite transition from physiologic adaptation to maladaptation.[4] Tissue inflammation, and its implication for tissue repair vs pathologic remodeling,[11] is in this way put into focus in the context of a sex-biased cardiac hypertrophic response associated with an increased risk for heart failure.

Outlook

The study by Gaignebet et al[4] inspires the prospect of an increasingly pathobiology-informed disease management paradigm. Today, correction of aortic stenosis often relies on invasive procedures, including transcatheter-based intervention or surgical aortic valve replacement. Establishing a prophylactic strategy that would limit disease progression and offer a cardioprotective solution is thus warranted. To date, hormone replacement therapy for postmenopausal women[12] or anti-inflammatory agents[9] have yet to be proven effective in clinical trials for cardiovascular disease. These experiences highlight the need for advancing individualized approaches that would target culprit disease pathways, optimally with distinctive tissue/cell specificity. An anti-CCN2–based therapy may, therefore, offer a valuable option against fibrotic disease, avoiding, in principle, pleiotropic effects of upstream regulators such as transforming growth factor-β.[10] In this regard, the anti-CCN2 antibody pamrevlumab is being tested in ongoing phase 3 clinical trials in the setting of idiopathic pulmonary fibrosis.[13] Along with developing therapeutic applications for cardiovascular medicine, knowledge gaps that need to be addressed include identifying mechanisms of cardiomyocyte gene regulation with or without dependency on estrogen or estrogen receptors; characterizing disease pathway drugable networks; and integrating expanding molecular information with complementary clinical parameters, including imaging and biomarkers. The ensuing comprehensive actionable framework would inform a precision health and disease approach for men and women.

Summary

Sex is a significant determinant of gender dimorphism, from normal physiology to disease phenotype and, ultimately, clinical outcomes. Implementation of rigorous methods of sex analysis in the design of research is paramount in fostering innovative discovery, improving scientific robustness, and prospectively ensuring health equality. Genomic medicine provides a powerful tool to understand the complex biology underpinning sex differences beyond the more traditional sex chromosome–centric perspective. Identifying disease pathways and developing matched therapies collectively offer an exciting future in addressing sex-biased disease.

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REFERENCES

1. Tannenbaum C, Ellis RP, Eyssel F, Zou J, Schiebinger L. Sex and gender analysis improves science and engineering. *Nature*. 2019;575(7781):137-146.
2. Naqvi S, Godfrey AK, Hughes JF, Goodheart ML, Mitchell RN, Page DC. Conservation, acquisition, and functional impact of sex-biased gene expression in mammals. *Science*. 2019; 365(6450).
3. Khramtsova EA, Davis LK, Stranger BE. The role of sex in the genomics of human complex traits. *Nat Rev Genet*. 2019; 20(3):173-190.
4. Gaignebet L, Kańduła MM, Lehmann D, Knosalla C, Kreil DP, Kararigas G. Sex-specific human cardiomyocyte gene regulation in left ventricular pressure overload. *Mayo Clin Proc*. 2020;95(4): 688-697.
5. Heart disease and stroke statistics—2020 update. American Heart Association website. https://professional.heart.org/professional/ScienceNews/UCM_505440_Heart-Disease-and-Stroke-Statistics—2020-Update.jsp.
6. Haider A, Bengs S, Luu J, et al. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome [published online December 26, 2019]. *Eur Heart J*. https://doi.org/10.1093/eurheartj/ehz898.
7. Oh JK, Ito S. Sex difference in left ventricular response to aortic stenosis [published online September 12, 2019]. *JACC Cardiovasc Imaging*. https://doi.org/10.1016/j.jcmg.2019.08.012.
8. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. *Science*. 2017;356(6342):1026-1030.
9. Suetomi T, Miyamoto S, Brown JH. Inflammation in nonischemic heart disease: initiation by cardiomyocyte CaMKII and NLRP3 inflammasome signaling. *Am J Physiol Heart Circ Physiol*. 2019;317(5):H877-H890.
10. Dorn LE, Petrosino JM, Wright P, Accornero F. CTGF/CCN2 is an autocrine regulator of cardiac fibrosis. *J Mol Cell Cardiol*. 2018;121:205-211.
11. Vagnozzi RJ, Maillet M, Sargent MA, et al. An acute immune response underlies the benefit of cardiac stem-cell therapy. *Nature*. 2020;577(7790):405-409.
12. Hormone therapy trials (HT). Women's Health Initiative website. https://www.whi.org/about/SitePages/HT.aspx.
13. Evaluation of efficacy and safety of pamrevlumab in patients with idiopathic pulmonary fibrosis [NCT03955146]. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03955146.