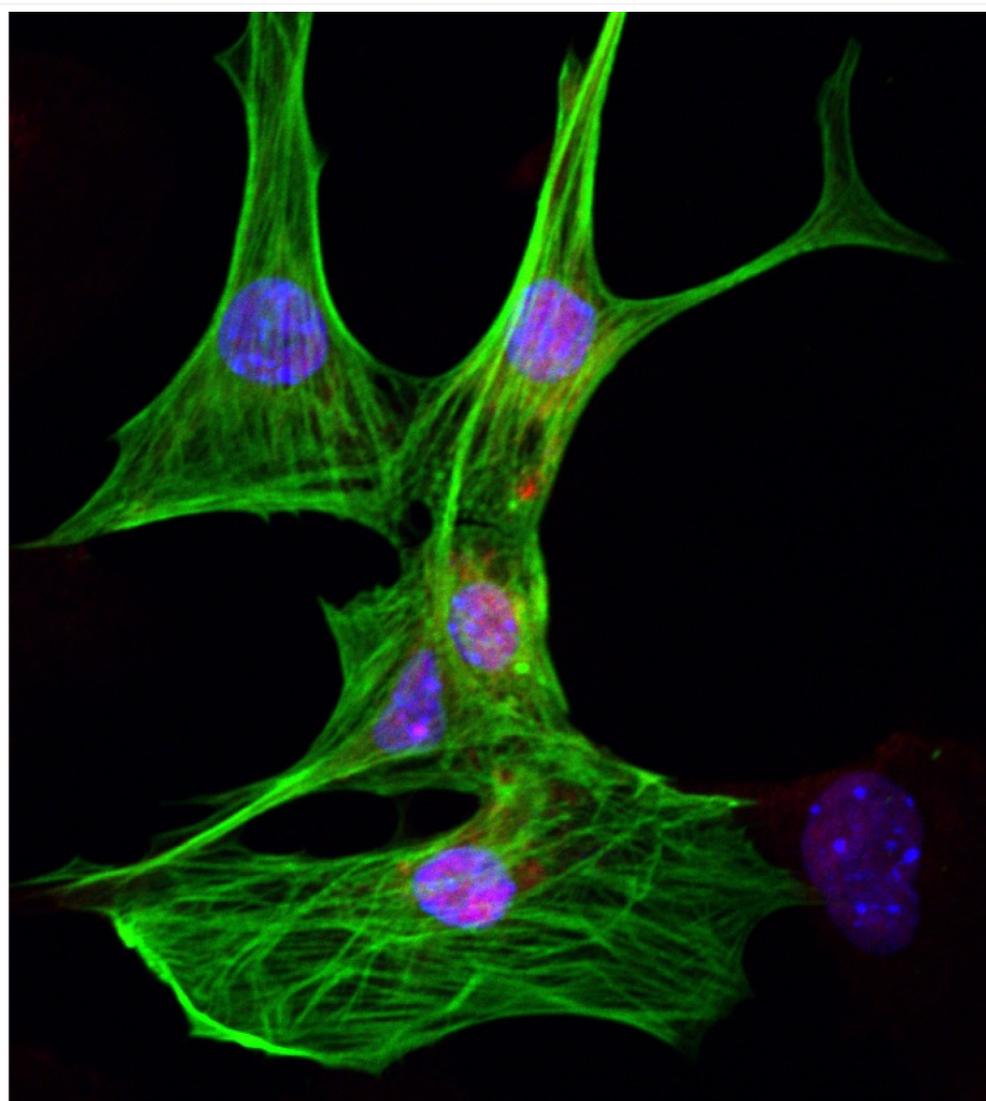


Journal Club

Highlighting recent, timely papers selected by Academy member labs

Hormones not the only drivers of sex disparities in heart health

Posted on October 29, 2021 (<http://blog.pnas.org/2021/10/hormones-not-the-only-drivers-of-sex-disparities-in-heart-health/>) by Carolyn Beans (<http://blog.pnas.org/author/cbeans/>)



(http://blog.pnas.org/wp-content/uploads/2021/10/TMY_A1bg_cardiomyocytesHeartHealthBlog.jpg)

These heart cells from a female mouse produce more of the protein A1BG (red) than male heart cells, possibly pointing to avenues for future heart disease interventions. Image credit: Wei Shi (University of North Carolina at Chapel Hill)

Often when it comes to disease, the sexes are not equal. [Dementia](https://www.alzheimers.org.uk/blog/why-dementia-different-women) (<https://www.alzheimers.org.uk/blog/why-dementia-different-women>), [chronic kidney disease](https://www.kidney.org/content/kidney-failure-risk-factor-gender-sex) (<https://www.kidney.org/content/kidney-failure-risk-factor-gender-sex>), and many other conditions disproportionately affect one sex or another. Heart disease is a complex case: Males are [more likely to suffer heart attacks](https://health.clevelandclinic.org/women-men-higher-risk-heart-attack/) (<https://health.clevelandclinic.org/women-men-higher-risk-heart-attack/>) at a younger age; females who suffer heart attacks have more difficulty recovering.

Sex hormones can [help explain \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4834858/\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4834858/) differences in heart health. “That’s been very well established,” says geneticist Frank Conlon of the University of North Carolina School of Medicine’s McAllister Heart Institute.

But now, Conlon, along with colleagues including Ileana Cristea of Princeton University in New Jersey, has discovered another factor: genes on the sex chromosomes themselves. The findings, [reported \(https://www.sciencedirect.com/science/article/abs/pii/S1534580721007668\)](https://www.sciencedirect.com/science/article/abs/pii/S1534580721007668) this month in *Developmental Cell*, could one day lead to new tools to treat heart disease.

In humans, heart disease is rooted in complex interacting factors, including genetics. “Even if you take into account economic disparities and cultural differences, there are certain genetic backgrounds which are predisposed,” says Conlon.

To account for this underlying genetic diversity, his team looked for sex differences in protein levels in adult mouse hearts across a hugely diverse range of mouse strains. They identified 1,379 proteins that differed in abundance by sex, including some already linked to cardiac disease in males or females. For some of these proteins, however, the sex bias flipped between mouse strains, a finding that further demonstrates that genetic background must be considered when testing for or treating heart disease, says Conlon.

A protein known as AIBG stood out for its especially high levels in female hearts. Through further experimentation, the team learned that this protein—whose function is not entirely clear—was essential to normal heart function in mouse females but relatively expendable in males.

The team also found that, in most cases, the amount of any particular protein did not correlate with the amount of its corresponding RNA, suggesting that molecular mechanisms that occur after RNA is transcribed, such as protein degradation, may contribute to male-female differences in heart health.

To identify the underlying causes of these disparities in protein abundance, the researchers needed to disentangle the effects of sex hormones from any possible effects of the genes on the sex chromosomes themselves. They bred four groups of mice, each with distinctive genotypes. One mouse group had ovaries and two X chromosomes. Another had two X chromosomes but testes—the result of an insertion of a testes-producing gene into a non-sex chromosome. The final two groups both contained an X and a Y chromosome, but—through manipulation of this same gene—one had testes and the other ovaries.

The team linked the levels of over 500 proteins to the presence of testes versus ovaries. The abundance of another 159 proteins, however, differed according to whether the mouse carried XX or XY chromosomes—confirming that genes on sex chromosomes play a role in heart protein levels.

Then, by studying protein levels in the hearts of developing mouse embryos, the researchers found that sex differences in protein levels exist even before sex organs form—further evidence that hormones are not the only driving factor.

In another experiment, the team discovered that the vast majority of genes that code for these sex-disparate proteins are not themselves on sex chromosomes. The team’s working hypothesis, says Conlon, is that one or more genes on the X chromosome may somehow control the abundance of these other proteins. Whatever the cause, the effect is dose dependent—two X chromosomes have a greater impact on protein levels than one.

This paper makes an important contribution, according to molecular biologist Leslie Leinwand of the University of Colorado Boulder, who has spent a quarter century exploring sex differences in the heart. “They are making a distinction between sex hormones and sex chromosomes, and that distinction isn’t often considered.”

This research is “groundbreaking” because it moves beyond the dogma that sex hormones cause sex disparities in cardiac disease, says Jose Pinto of the Florida State University College of Medicine, a muscle biophysicist and biochemist who studies regulation in cardiac muscle. “The major implication,” he says, “is that we as investigators would have to think twice when designing studies to look at sex difference, and not only for cardiac disease but any disease.”

Indeed, Conlon’s team is now testing whether genes on sex chromosomes may similarly trigger sex disparities in other diseases. He expects that the findings will “translate to other organ systems.” They’re also searching for the specific genes on the X chromosome that prompt these differing protein levels. Uncovering these genes could ultimately point to sex-tailored treatment options.

Leinwand agrees that therapeutic applications are a possibility. “When people talk about personalized medicine approaches,” she adds, “I think biological sex is one of the biggest ones that should be tackled.”

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Online ISSN 1091-6490

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