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Y Not? Sex Chromosomes May Modify Sexual Dimorphism in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a progressive and fatal pulmonary vascular disease more likely to impact females than males, but it is complicated by a possible survival advantage for females (1–5). The precise biologic underpinnings driving this difference remain incompletely understood. However, several recent studies have explored the role of sex hormones and their metabolites in PAH pathogenesis (recently reviewed by Foderaro and Ventetuolo [6]) (7–9). In fact, progress in the study of sex hormones has launched a new era of therapeutic development centered on estrogen modification in PAH, including several human trials (10).

Despite the compelling association of sex with PAH, studies to date have not explored the role of the sex chromosomes (chromosomes XX in females and XY in males). Although sex hormones are undoubtedly important, foundational differences between females and males also anchor in the inherent genetic differences as determined by the genes on the sex chromosomes. However, determining the contributions of sex hormones versus sex chromosomes in experimental and human conditions is complicated because they are intimately linked—the sex chromosomes influence the types and levels of sex hormones. Fortunately, tools for study do exist, such as the four core genotypes (FCG) murine model system. This system employs two different genetic variations: 1) a Y chromosome unable to direct male gonad development owing to deletion of the *Sry* (sex-determining region Y) gene, allowing production of XY female mice; and 2) the insertion of an *Sry* transgene into chromosome 3, such that XX male mice may develop (11). The FCG model system thus creates the opportunity to independently segregate gonadal type from the sex chromosome complement. Studies using the FCG model system have shown that phenotypic traits such as metabolic syndrome, with increased adiposity and insulin

resistance, are influenced by XX and XY (recently reviewed by Link and Reue [12]).

The Y chromosome is the smallest of the 46 chromosomes and contains the fewest genes (approximately 568), of which only 71 are known to encode proteins. Most but not all proteins are unique to the male sex and transmitted only via the Y chromosome (13). For example, the *SRY* gene is critical to determining male sex, whereas others, such as *USP9Y* (ubiquitin-specific peptidase 9) and *DDX3Y* (Y-linked DEAD-box helicase 3), contribute to male fertility via spermatogenesis. These and other Y chromosome-specific genes are ubiquitously expressed in multiple cell and tissue types during development and beyond (14). In addition, emerging data suggest that the Y chromosome significantly contributes to systemic diseases, including immunity and the inflammatory response, blood pressure regulation, and coronary atherosclerotic heart disease (recently reviewed by Maan and colleagues [15]).

In this issue of the *Journal*, Umar and colleagues (pp. 952–955) present work exploring the significance of the sex hormone complement in hypoxia-induced pulmonary hypertension (PH) using the FCG and XY* model systems (16). Umar and colleagues found that, regardless of gonadal sex, under conditions of hypoxia, XY mice developed less severe PH. This finding raised a logical question: Was the Y chromosome protective, or was the presence of only one X chromosome protective, or both? To answer this question, they employed an additional model, the XY* model, and determined that the presence of a Y chromosome conferred the protection. These intriguing results support the concept that factors present on the Y chromosome prevent the development of hypoxic PH rather than a susceptibility conferred by the X chromosome. But what are those factors provided by the Y chromosome?

As noted above, the Y chromosome influences many phenotypic traits beyond sex and sex determination. In exploratory analyses of retrospective data of publicly available datasets, Umar and colleagues found reduced expression of *KDM5D*

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(lysine demethylase 5D) and *UTY* (ubiquitously transcribed tetratricopeptide repeat containing, Y-linked), in PAH lungs compared with control lungs. As they discuss, downregulation of these two genes is associated with loss of cellular control and a proliferative cellular milieu—supporting the hypothesis that loss of Y chromosome–derived genes contributes to the altered cellular processes that result in PAH pathogenesis (17).

The data presented in the study by Umar and colleagues invite several intriguing questions. First, what are the specific genetic factors driving the Y chromosome's influence? This remains an unanswered question because the *in silico* data they present are limited to existing published datasets for which detailed phenotypic information was not available, and importantly, the sex of the subjects from whom expression data were derived was not provided. Second, analyses of available gene expression datasets are confounded by difficulties in discerning expression differences between gene paralogs within a given species; this is relevant because *KDM5D* and *UTY* have functionally similar gene paralogs on other chromosomes, including the X chromosome (e.g., *KDM5C*). It is possible that expression variations according to phenotype were modified by paralog gene expression on chromosomes other than Y (18). Third, although the animal model data are compelling, it is important to note that hypoxic models of PH are not a definitive representation of PAH, and hypoxia-associated PH does not have a particular tendency to affect one sex over the other. Fourth, it is difficult to reconcile these findings with previous work by Aldred and colleagues, in which they found a high prevalence of mosaic loss of the X chromosome in the lung tissue of female patients with end-stage PAH (19).

In summary, Umar and colleagues have introduced a novel area for exploration in pulmonary hypertensive vascular disease. Future studies should account for sex hormones, the sex chromosome complement, and their interaction. To this end, studies employing the FCG and XY* models in different PH model systems may be helpful. Also, prospective gene and gene expression analyses of X and Y chromosome–derived genes from germline, lung, and right ventricular tissue sources should be done to explore relationships with known pathways in PH, such as transforming growth factor- β superfamily signaling, and new ones. Finally, the potential role of sex chromosomes in right ventricular adaptation to right ventricular stress remains an area of opportunity. Many exciting studies will soon follow—Y didn't we think of this sooner? ■

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