and coworkers should be examined forensically against clinically important outcomes in future studies. ■

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A dUTY to Protect: Addressing "Y" We See Sex Differences in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a progressive disease, characterized by elevated pulmonary arterial pressure and subsequent right heart failure. These changes result from pulmonary vasculature wall thickening and remodeling. Pathogenic vascular remodeling stems in part from endothelial cell dysfunction and vascular smooth muscle cell proliferation (1). Pulmonary vascular disease progression is also driven by increased inflammatory cells and mediators, such as macrophages and cytokines, which promote further pathologic remodeling (2). Interestingly, the epidemiology of PAH reveals a fourfold greater disease prevalence in females than males, accompanied by a reciprocal increase of disease severity in males versus females (3). Insights into the sexual dimorphism observed in PAH may lead to the development of better therapeutics, as current therapies are not curative (4). But, the mechanism(s) underlying these gender differences remain poorly understood (5).

Guided by a historical focus on the role of sex hormones in PAH, a puzzling yet crucial finding has emerged: estrogen prevents disease experimentally, while clinically, females have higher disease incidence (3). Thus, sex hormone differences alone may not adequately explain the female predominance of PAH development. Accordingly, Umar and colleagues looked to chromosomal differences between the two sexes instead. Previously, they found a protective role of the Y chromosome (ChrY) in PAH, independent of gonadal hormones (6). At the same time, Yan and colleagues described pathogenic activity of the ChrY gene *sry* in PAH via regulation of BMPR2 gene expression in fibroblasts—findings that also suggested a role of *sry* in PAH gender differences (7). But, *sry* alone could not alone explain ChrY-dependent protection, because XY *female* mice lacking *Sry* were still protected against PAH when compared with XX females (6).

In this issue of the *Journal* (pp. 186–196), this group delved deeper to understand how the ChrY confers protection against the development of PAH (8). The authors concluded that the ChrY gene, *uty* (ubiquitously transcribed tetratricopeptide repeat containing, y-linked), is responsible for this protective role, and identified downstream inflammatory mediators as important therapeutic targets. The group first found ChrY genes that were expressed in mouse lung tissue and individually knocked down each gene in the lungs of gonadectomized hypoxic mice. Of the four genes they investigated, only knockdown of *uty* resulted in PAH development.

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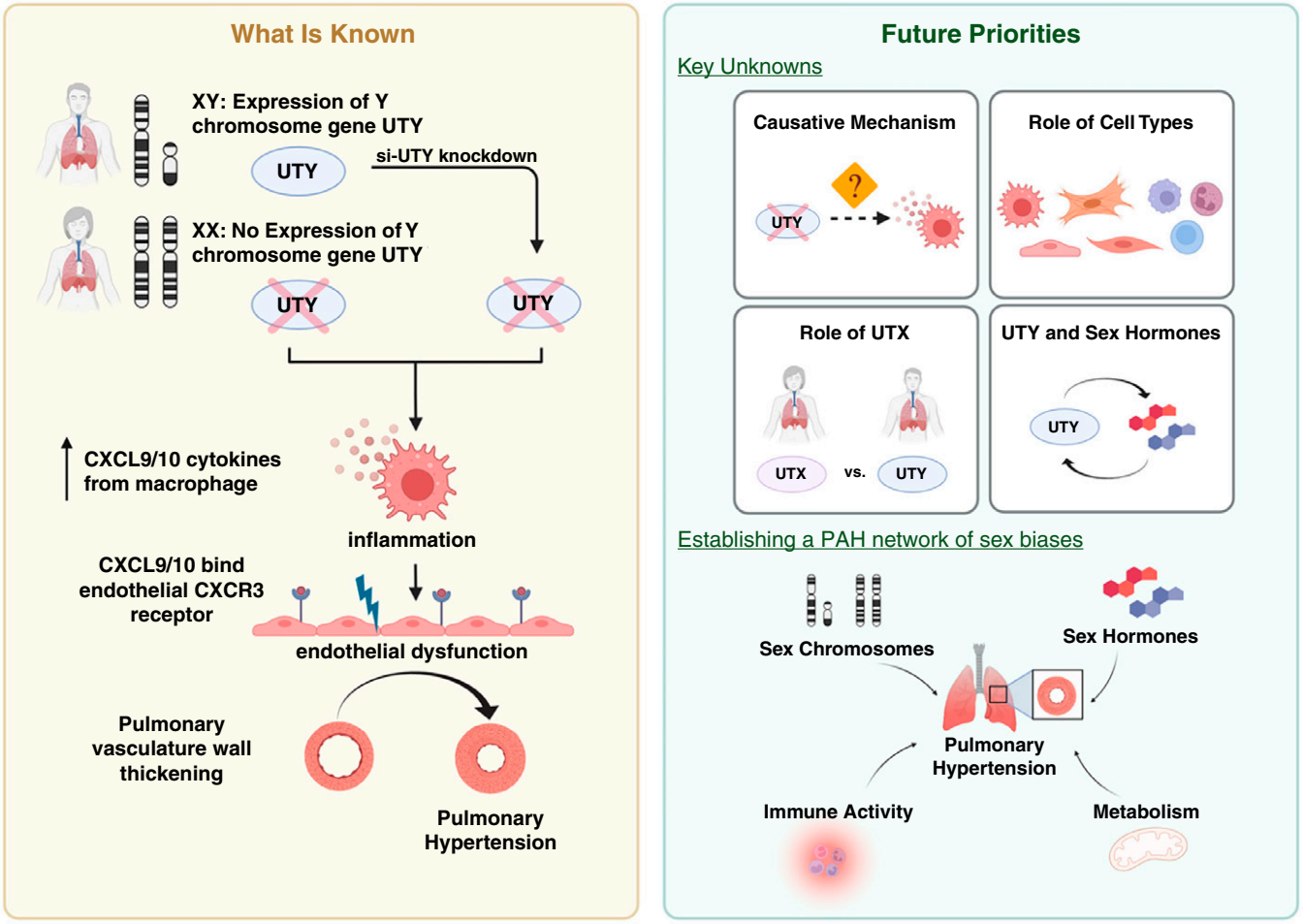

Figure 1. Decreased UTY (ubiquitously transcribed tetratricopeptide repeat containing, y-linked) causes increased inflammation via upregulation of proinflammatory cytokines CXCL9/10 (C-X-C motif chemokine ligand 9/10) release from macrophages. Binding of these cytokines to CXCR3 (C-X-C motif chemokine receptor 3) results in endothelial dysfunction and subsequent development of pulmonary arterial hypertension (left panel). Further understanding of sex biases in physiologic and pathologic processes may provide insight necessary for the successful development of gender-based targeted therapeutics (right panel). Created with BioRender.com. PAH = pulmonary arterial hypertension; UTX = female paralog of UTY.

RNA sequencing analysis yielded proinflammatory cytokines CXCL9 (C-X-C Motif Chemokine Ligand 9) and CXCL10 as top genes of interest. Both their *in vitro* and *in vivo* findings corroborated that decreased UTY expression in macrophages upregulated the proinflammatory cytokines CXCL9 and CXCL10. These cytokines, which are also robustly upregulated in lungs of female PAH patients, triggered endothelial dysfunction by binding the CXCR3 (C-X-C Motif Chemokine Receptor 3) receptor and promoting PAH pathophenotypes (Figure 1).

Overall, this work describes a potentially important discovery of a protective role of the UTY-CXCL9/10 axis in PAH, independent of sex hormone alterations. Considering expression patterns of UTY documented in both lung tissue and macrophages, these findings offer molecular insight into how ChrY can directly regulate gene expression in somatic cells and invoke a greater complexity in PAH sex differences than previously appreciated (9, 10). Additionally, blocking CXCL9/10 activity prevented PAH, representing a promising step forward for the development of targeted and gender-specific therapeutics.

However, these key findings raise several new questions to be addressed by future studies. First, the causative mechanism linking reduced UTY expression and upregulation of proinflammatory cytokines CXCL9 and CXCL10 remains unclear. Although UTY is a known member of the Jumonji family of histone 3 lysine 27 (H3K27) demethylases, Cunningham and colleagues found that UTY did not influence methylation levels in the lung, consistent with prior studies showing that UTY retains low levels of catalytic activity (11). Thus, future work is needed to define how UTY controls this downstream chemokine axis. Second, while evidence is suggestive of both macrophage and endothelial cell involvement, more precise proof is needed to show that these cell types and potentially others are essential for the protective effects of the UTY-CXCL9/10 axis. Given the pleiotropic roles of the CXCL9/10 chemokines even beyond inflammation, it is possible that other genetic, environmental, and even metabolic perturbations may be relevant to this disease pathway (12). Third, it is also known that UTY carries a high degree of homology with UTX, the female paralog of UTY (10). Thus, assessing the role of UTX in PAH may lead to further insight into gender differences in this disease. Finally, while Cunningham and

colleagues present evidence that UTY can act independently of sex hormones, a more nuanced interplay between UTY and sex hormones is possible and even likely in PAH. Future work to define that complex mechanism may help to unravel the still unsolved estrogen paradox as well as the clinical observation of greater disease severity in males (3).

Ultimately, the fundamental contributions of this study could pave the way for a more precise understanding of the complex PAH network of sex biases across genetic, environmental, immunologic, and metabolic factors (Figure 1; 1, 6, 13, 14). If successful, such endeavors bring us closer to precision medicine in PAH and long-awaited, gender-based clinical treatment strategies in this challenging disease. ■

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Chronic Obstructive Pulmonary Disease–Obstructive Sleep Apnea Overlap: More Than a Casual Acquaintance

In this issue of the *Journal* (pp. 197–205), Sterling and colleagues (1) report on the impact of positive airway pressure (PAP) therapy in patients with overlap syndrome.

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) each affect at least 10% of the adult general population and thus, the two disorders occurring together, often referred to as the overlap syndrome, is likely to be common based on chance association alone. Some factors relating to COPD such as malnutrition leading to low body mass, hyperinflation associated with a low diaphragmatic position (increased "tracheal tug"), reduced REM sleep, upright sleep position, and potentially age factors can decrease the likelihood of OSA. Conversely, other variables such as weight gain, cigarette smoking, medications, rostral fluid shifts in recumbent position, higher diaphragmatic position, etc., can predispose to OSA (2). Additionally, OSA predisposes to lower airway inflammation, which in turn may promote the development of COPD (Figure 1). Both COPD and OSA generate local and systemic inflammatory responses that may lead to cardiovascular morbidity and, thus, the overlap syndrome should be expected to be associated with an increased likelihood of cardiovascular disease compared with either disorder alone (3). While pulmonary hypertension has long been recognized as a common finding in overlap patients, likely due to more severe diurnal hypoxemia than patients with COPD alone (4), epidemiological data on the prevalence of other co-morbidities are limited. However, Kendzerska and colleagues

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