injury, the severity of the brain injury, levels of consciousness, and the time after injury (12, 13). Traumatic brain injury is a heterogeneous condition and has been reported to contribute to Alzheimer's disease and frontotemporal dementia independently of bacterial infection (14, 15). These could be confounding factors, and future studies will ideally be undertaken in critically ill patients not affected by brain injury. Careful serial assessment of cognitive function and neurological status before and also repeatedly during and after intensive care treatment and pneumonia will be critical to correlate bacterial infection with A β and tau oligomer neurotoxicity.

Although it may seem that this study raises more questions than answers, it also shows how much is yet unknown. A more detailed assessment of the nature and aggregation status of A β and tau proteins beyond A11 and T22 reactivity is crucial and should reveal additional insights about these biomarker dynamics in critically ill patients. Longitudinal biomarker assessment in large cohorts and additional *in vitro* toxicity studies would address whether nosocomial pneumonia is indeed a risk factor for cognitive symptoms related to post-intensive care syndrome. Although Lin and colleagues raise a provocative hypothesis, if bacterial infection is indeed related to Alzheimer's disease-like biomarker changes and symptoms in post-intensive care syndrome, interventions to block or reverse these processes could be of great benefit to these patients (5). ■

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The Y Chromosome Takes the Field to Modify BMPR2 Expression

You can observe a lot by just watching.

—Yogi Berra

The term estrogen paradox is frequently used in pulmonary arterial hypertension (PAH) to describe the phenomenon of less severe

hemodynamic alterations and increased survival in women despite their increased susceptibility to developing this disease (1). For those only vaguely familiar with this term, the lack of a uniting theory can seem confusing and muddled. For those studying the estrogen paradox in PAH, the data are also confusing and muddled (1, 2). This can be attributed in part to the multifactorial, pleiotropic, and temporal complexities of sex, sex hormones, and disease development. Despite being heavily studied, the sex disparity in PAH lacks a precise and unifying mechanism to account for both sides of the estrogen paradox, as well as guidelines for a sex-based treatment approach in patients.

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Figure 1. Simplified overview of established and purported factors contributing to sexual dimorphisms in pulmonary arterial hypertension (PAH). Note cross-talk between individual components (arrows). Genetic factors determined by somatic chromosomes may contribute as well. DHEA = dehydroepiandrosterone.

Attempts to understand the contribution of sex to PAH have primarily relied on the investigation of 17β -estradiol in the development of and protection against PAH. On the basis of data suggesting stimulatory effects of 17β -estradiol on PAH development, a phase 1 trial using the aromatase inhibitor anastrozole in male and postmenopausal female patients with PAH was conducted (3). This trial demonstrated feasibility and safety, although effects were variable between patients, and some participants had evidence of worsening right ventricle function (3, 4). Meanwhile, other studies identified a protective role for 17β -estradiol against the development of PAH, mediated by attenuation of pulmonary vascular remodeling and preservation of right ventricle structure and function (1, 2). Still other approaches set out to determine the role of estrogen metabolites, with some studies showing that 2-methoxyestradiol promotes protective, vasorelaxant, antiproliferative, and proapoptotic responses in pulmonary vascular cells, whereas other studies suggested that 16α -hydroxyestrone has the opposite effect (1). It has been postulated that the imbalance of these metabolites and the enzymes that generate them (CYP1B1 [cytochrome P450 1B1] and catechol-*O*-methyltransferase) could be a contributing factor for the sex disparity in PAH (5).

More recently, nonhormonal factors such as immune-mediated mechanisms and contributions of sex chromosomes have been implicated as modifiers of PAH development. For example, a recent study linked regulatory T-cell-dependent protective immune responses to a less severe pulmonary hypertension phenotype in women (6). Recent work by Umar and colleagues demonstrated that mice with an XY complement of chromosomes (regardless of sex) develop less severe hypoxia-induced pulmonary hypertension than XX complement mice, suggesting the Y chromosome is protective (7). Building on this latter finding, in this issue of the *Journal*, Yan and colleagues (pp. 1581–1583) revisit the Y chromosome and describe a novel and putative transcriptional target of SRY (sex-determining region Y) in adult male dermal fibroblasts (8): BMPR2 (bone morphogenetic protein receptor 2), an “old friend” and “big player” in PAH and vascular biology (9). Females do not have a Y chromosome

and therefore lack SRY; a protective role of this gene against the development of PAH therefore makes conceptual sense.

A regulatory connection between SRY and BMPR2 is a logical and novel finding building on the roles of SRY and BMP signaling in gonadogenesis and development (9–12). SRY, a member of the SOX protein family, is necessary and sufficient to determine male sex by inducing genital ridge formation followed by testes development (11). Likewise, BMP4 (which signals through BMPR2) plays a role in proper primordial germ cell segregation along the genital ridge (13), suggesting a potential for cross-talk between these pathways. Furthermore, RNA-Seq analysis in chicken embryos undergoing gonadal sex differentiation revealed that *BMPR2* is enriched in male gonads (14). Another possible location for interaction between SRY and BMP signaling occurs in the brain, where both mediators have been linked to formation and maintenance of dopaminergic neurons (15, 16).

Precedence exists that SRY has a role outside of sex determination to modify disease development. For example, SRY has been implicated as an important component in male cancer stem cells (17), and overexpression of SRY in the male brain has been linked to Parkinson’s disease, autism, and attention-deficit/hyperactivity disorder (15).

The current work by Yan and colleagues provides preliminary evidence of a direct regulatory connection between SRY and BMP signaling. Similar to all novel studies, this work raises many new questions: Is the SRY-BMPR2 connection present and relevant in pulmonary vascular cells? Do lung-derived fibroblasts exhibit a similar expression level of SRY as the dermal fibroblasts employed in the current study? Are there sex differences in BMPR2 expression in dermal fibroblasts derived from control patients and/or patients with PAH to begin with? How does the presence of *BMPR2* mutations affect this potential signaling axis? Smad 1/5/8 signaling was not affected in the current study, so which pathway(s) are regulated by SRY-BMPR2? Last, female fibroblasts likely do not have an SRY-binding site, so do they have an alternative evolutionarily conserved compensatory mechanism to regulate BMPR2 expression?

Despite these questions, the work by Yan and colleagues is an exciting new finding with potential ramifications not only in developmental biology but also for better understanding the sex disparity of PAH.

Only further study will identify whether SRY is indeed able to regulate BMPR2 expression in PAH, and whether this translates into protective effects *in vivo*. This also demonstrates that the term estrogen paradox does not sufficiently describe the sexual dimorphisms of PAH, as these dimorphisms likely are determined not just by estrogens alone (Figure 1). Ultimately, the answer to understanding the basis of the sexual dimorphisms in PAH likely resides in embracing and integrating the complexity of the many factors contributing to sex/sex differences in this disease. For example, the dynamic combination of estrogen receptor expression and activity, estrogen metabolites, and nonhormonal factors all contribute to 17 β -estradiol's pleiotropic effects at a cell- and tissue-specific level. Furthermore, each of these elements changes throughout the lifespan of an individual and throughout the course of a disease. The most powerful approach to identify which populations of patients with PAH will most benefit from stimulation or suppression of sex-based pathways will integrate the contributions of sex hormones, sex chromosomes, somatic chromosomes, metabolites, and nonhormonal factors. The field is complex, but we have made great progress and will learn a lot by watching and observing the interplay between these modulators. ■

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