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In Gender-Based Outcomes, Sex Hormones May Be Important But It Is in the Genes

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In this issue, Guidry et al presents an elegant study on gender-associated susceptibility to pneumonia and mortality from 2291 ICU patients with trauma and non-trauma related etiology of acute illness in a prospective cohort (1). The study demonstrates moderate but evident benefit of female gender in the trauma cohort manifesting in improved survival and lower susceptibility to pulmonary infections as compared to males. They also demonstrate greater blood levels of admission cytokines in males than females (1). Whereas observations on gender-biased outcomes remain mixed, studies have demonstrated a female benefit in the critically ill with increasing consistency (1 and refs within). Guidry's current study further supports this notion.

Despite the prospective design and thorough and careful analytical approach, the study also reflects the unavoidable and inherent difficulties of clinical investigations addressing this question. The lack of gender effect in the non-trauma cohort is most likely the result of mixed etiology and varying stages of acute illness at enrollment, which easily can confound the impact of gender. Even in the trauma cohort, which was sufficiently powered and where the onset of pathology is well-defined, the differences in study site-related comorbidity, injury severity and initial physiological and organ function status may blunt and confound sex effects.

The relatively small degree of sex-related differences in outcome and the inherent difficulties of clinical studies raise several questions. Are the relatively small sex-based differences important clinically? Should we stratify more the cohorts or broaden the tested parameters? What is the underlying mechanism of female protection? Trying to answer these questions may be premature, because gender studies neglected to address the potential contribution of sex-chromosome differences to gender-biased inflammation (2;3).

Males carry only one, the maternal X chromosome, whereas females carry both parental X chromosomes. Thus, due to the X-linked inheritance pattern, X-linked polymorphisms

producing a clinical phenotype always impact more males than females in the population (3). Additionally, females present random X chromosome inactivation, which results in mosaic cellular expression of X-linked polymorphic genes and proteins (2;3). The X chromosome is rich in polymorphic immuno-modulatory genes and female cellular mosaicism for cells activated at different degree may “broaden” as well as “buffer” inflammatory and injury responses (3). The notion that female cellular mosaicism is a contributing protective mechanism is attractive since sex hormone differences alone do not fully account for sex-biased outcomes in animal models or clinical studies (1;4-6). To illustrate this genetic concept, I would like to present the potential practical impacts of X-linked mutations on the Guidry study using the X-linked IRAK1 variant haplotype as an example.

IRAK1, (IL1R-associated kinase) is a regulatory protein of the TLR/MyD88 complex involved in cell activation and cytokine production, including TNF- α , IL-6 and IL-10 via NF κ B, MAPKs and Stat3 (7-9). The variant IRAK1 has a range of 25-70% population frequency depending on race (10;11). The variant IRAK1 haplotype displays a sustained increase in kinase activity resulting in increased cell activation and cytokine production upon TLR stimuli. Independent clinical studies (7;12) on ICU patients demonstrated that subjects with the high activity IRAK1 variant (hemizygous males and homozygous females) present increased incidence (30-50%) of pulmonary infections, longer need for ventilation support, septic shock and in-hospital mortality as compared to subjects with the “WT” variant. Importantly, these human studies, although not focusing on the gender aspect, suggested that heterozygous females with cellular mosaicism for the expression of the “WT” and variant IRAK1 protein present a similar outcome to “WT” subjects (7;12). Accordingly, recent mouse investigations also demonstrated improved outcome in septic females with cellular mosaicism for IRAK1 expression (13).

So what happens if we extrapolate these previous observations on the IRAK1 variant to the current study? The Guidry cohort racial distribution was (%) 81 white, 12 black and 7 “other”. The frequency of the IRAK1 variant protein is 20-30 % in whites and blacks (10;11). Thus, assuming a 25% IRAK1 variant frequency in the Guidry cohort the expected IRAK1 phenotype distribution stratified by gender is the following. Males: 25% hemizygous affected and 75% unaffected “WT”; Females: 6 % homozygous affected, 56% unaffected “WT” and 38% likely unaffected heterozygous (i.e., mosaicism for the variant). If the IRAK1 variant contributed, at least in part, to the clinical course of the Guidry cohort, and it likely did, then its impact was four-fold greater on males than females (25% vs 6.3%). Furthermore, due to the greater number of males in the trauma cohort this percentage difference accounts to 256 affected male but only 24 affected female patients in the trauma cohort (tenfold difference). This overrepresentation of the IRAK1 variant in males is consistent with the increased admission cytokine levels, more frequent pulmonary infections and worsened mortality observed in the study (1;7;12). Thus, it is quite possible that the female advantage demonstrated in the Guidry study, and presumably other studies of similar design, is related, at least in part, to the increased representation of the IRAK1 variant among males in the cohort.

IRAK1 polymorphisms is only one example and other X-linked immuno-modulatory genetic variants are expected to contribute to or confound the observations through increased representation of X-linked risk alleles in males. At the same time, whereas cellular mosaicism for the IRAK1 variant seems to be advantageous in acute inflammation, mosaicism for other X-linked risk alleles may be disadvantageous. If this were the case, then mosaic status would blunt or switch the direction of female sex advantage. In support of this notion, X chromosome mosaicism has been implicated in increased female susceptibility to auto-immune diseases (14;15).

In summary, increasing number of investigations including the current study by Guidry et al (1) provides evidence that sex impacts the clinical course of acute illness. However, in order to elucidate the full-scale of sex effects in the severely ill, stratification by gender alone may not be sufficient. It is due time to start testing for and stratify by X-linked polymorphisms and X chromosome mosaicism when investigating gender-bias in the critically ill (3;5;13). Only this approach will produce a more complete and nuanced understanding of the impact of gender dimorphism in disease processes.

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Reference List

1. Guidry CA, Swenson BR, Davies SW, et al. Sex and diagnosis dependent differences in mortality and admission cytokine levels among patients admitted for intensive care. *Crit Care Med*. 2014 in press.
2. Libert C, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. *Nat Rev Immunol*. 2010; 10:594–604. [PubMed: 20651746]
3. Spolarics Z. The X-files of inflammation: cellular mosaicism of X-linked polymorphic genes and the female advantage in the host response to injury and infection. *Shock*. 2007; 27:597–604. [PubMed: 17505297]
4. Klein SL. Immune cells have sex and so should journal articles. *Endocrinology*. 2012; 153:2544–2550. [PubMed: 22434079]
5. Chandra R, Federici S, Nemeth ZH, et al. Female X-chromosome mosaicism for NOX2 deficiency presents unique inflammatory phenotype and improves outcome in polymicrobial sepsis. *J Immunol*. 2011; 186:6465–6473. [PubMed: 21502376]
6. Sperry JL, Vodovotz Y, Ferrell RE, et al. Racial disparities and sex-based outcomes differences after severe injury. *J Am Coll Surg*. 2012; 214:973–980. [PubMed: 22521668]
7. Arcaroli J, Silva E, Maloney JP, et al. Variant IRAK-1 haplotype is associated with increased nuclear factor-kappaB activation and worse outcomes in sepsis. *Am J Respir. Crit Care Med*. 2006; 173:1335–1341.
8. Gottipati S, Rao NL, Fung-Leung WP. IRAK1: a critical signaling mediator of innate immunity. *Cell Signal*. 2008; 20:269–276. [PubMed: 17890055]
9. Huang Y, Li T, Sane DC, Li L. IRAK1 serves as a novel regulator essential for lipopolysaccharide-induced interleukin-10 gene expression. *J Biol Chem*. 2004; 279:51697–51703. [PubMed: 15465816]
10. Ishida R, Emi M, Ezura Y, et al. Association of a haplotype (196Phe/532Ser) in the interleukin-1-receptor-associated kinase (IRAK1) gene with low radial bone mineral density in two independent populations. *J Bone Miner Res*. 2003; 18:419–423. [PubMed: 12619925]

11. Kaufman KM, Zhao J, Kelly JA, et al. Fine mapping of Xq28: both MECP2 and IRAK1 contribute to risk for systemic lupus erythematosus in multiple ancestral groups. *Ann Rheum Dis.* 2013; 72:437–444. [PubMed: 22904263]
12. Toubiana J, Courtine E, Pene F, et al. IRAK1 functional genetic variant affects severity of septic shock. *Crit Care Med.* 2010; 38:2287–2294. [PubMed: 20890200]
13. Chandra R, Federici S, Nemeth ZH, et al. Cellular mosaicism for X-linked polymorphisms and IRAK1 expression presents a distinct phenotype and improves survival following sepsis. *J Leukoc Biol.* 2013
14. Forsdyke DR. X chromosome reactivation perturbs intracellular self/not-self discrimination. *Immunol. Cell Biol.* 2009; 87:525–528.
15. Selmi C, Brunetta E, Raimondo MG, Meroni PL. The X chromosome and the sex ratio of autoimmunity. *Autoimmun Rev.* 2012; 11:A531–A537. [PubMed: 22155196]