Cell

Making a Difference in Pain

Sexual dimorphism can be seen at many levels across the animal kingdom. In humans, it is still surrounded by much controversy and myth. While many sex-specific differences are remarkably obvious, others are subtle, complex, or even puzzling. Psychological and socio-cultural factors can also play a role by heavily influencing the perception of these differences. Take pain, for instance.

The old tale that women can handle pain better than men, perhaps because they endure labor pain, is far from being backed up by science. In fact, numerous studies have reported a higher prevalence of chronic pain and greater pain sensitivity among women as compared to men (Mogil, 2012). It is likely that there is a psychological component to this differential pain behavior, perhaps related to gender role expectations and to the fact that women seem to be more likely to seek health care than men. While these reports convincingly show that women are more sensitive to pain overall, the greatest scientific challenge is to untangle and decode the various elements implicated in pain behavior and the biological mechanisms underlying the differences between sexes. This endeavor is further complicated by the female hormonal cycle, which certainly impacts pain sensitivity. It is therefore somewhat intuitive to think about a common pain circuit between sexes that would be further modulated by circulating hormones. Indeed, this has been the pervasive view in the pain research community.

The recent discovery that pain hypersensitivity in female and male mice depends on different types of immune cells challenges this notion and offers new insights as to why men and women respond differently to pain (Sorge et al., 2015). The jumping off point for this study was the finding that inflammatory and neuropathic pain in male, but not female, mice depended on the Toll-like receptor 4 (TLR4) (Sorge et al., 2011). The team led by Jeffrey Mogil and Michael Salter now reports that the cell type where this receptor is expressed, the microglia, does not appear to be involved in neuropathic pain processing in female mice. Rather, females preferentially use an alternative pathway dependent on resident T-lymphocytes. In this study, when male mice were administered microglial inhibitors following nerve injury, their pain sensitivity was significantly reduced, while no improvement was seen in female mice (Sorge et al., 2015). As microglia have been regarded as promising targets to treat pain, these findings carry far-reaching clinical implications for pain management and analgesic drug development. Like all exciting discoveries, this study raises more questions than it answers—the most obvious being how these sex differences relate to disease and whether they can help explain why pain-related and auto-immune disorders, many of which involve T cell hyperactivity, are more prevalent in women (Mogil, 2012). A large-scale gene regulatory study led by the laboratory of Howard Chang shed some light on this conundrum (Qu et al., 2015). Here, the authors mapped open chromatin sites in human immune T cells, isolated from standard blood draws to generate a high-resolution regulome in a snapshot in time within a single individual. Gender was by far the most significant source of T cell chromatin variability; hundreds of target genes were found to be differentially regulated between male and female T cells, including many autosomal genes associated with immune function and autoimmune diseases.

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Taken together, these two studies indicate a broader than anticipated, and far more intricate, repertoire of immune-related sex differences. Historically, medical research has been conducted predominantly on males, and many studies still fail to appreciate the importance of sexual dimorphism both in experimental design and data interpretation. A painful, but valuable, lesson from this recent string of discoveries is that equal representation of both sexes in pain research, or in any biological discipline for that matter, is of utmost importance and that research performed mostly on males cannot be applied to both sexes in a clinical setting.

With the growing appreciation that sex differences in medicine are extensive, there's now little doubt that men and women may require different strategies for the treatment of pain and other conditions. As personalized medicine takes political and scientific spotlight, hopefully sex and gender-based medicine will follow.

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