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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Estrogen-Mediated Effects Underlie Gender Bias in Inflammatory Bowel Disease

The gastrointestinal tract is continuously exposed to a myriad of food antigens and symbiotic microflora, thus modulation of the inflammatory response is tightly regulated to prevent aberrant immune activation and chronic inflammation. However, in individuals with a genetic and environmental predisposition (eg, altered microbiota, viral or bacterial infection, chemical additives, or pollutants), regulation of intestinal inflammation is impaired. This condition leads to a chronic relapsing immune activation against luminal antigens, also known as inflammatory bowel disease (IBD).[1] IBD consists of 2 main types, Crohn's disease (CD) and ulcerative colitis (UC), and typically is characterized by debilitating symptoms such as bloody diarrhea, weight loss, and fatigue.[2] Currently, IBD is emerging as a growing health care problem in industrialized countries, with a prevalence of 0.5% in the general Western population.[3] This was equal to almost 3.5 million patients in the United States and Europe, with a direct health care cost of more than US $10 billion annually and an invaluable impact on the emotional, financial, and social state of the patients and their families.[3]

Symptoms of IBD fluctuate considerably over time and often flare at times of hormonal changes, such as puberty, pregnancy, and menopause,[2] suggesting a potential involvement of steroid hormones such as 17β estradiol (estrogen), prolactin, and testosterone in the pathogenesis of this disease. As reported for several other chronic inflammatory diseases,[4] IBD also shows a gender bias, with females slightly more prone to develop CD, whereas males are more likely to develop UC.[5] Until now, the molecular and cellular mechanisms underlying this gender bias were unclear, although sex-specific differences in the immune system together with hormonal influence on the inflammatory response were thought to play a major role.

Data from Goodman et al[6] published in this issue of *Cellular and Molecular Gastroenterology and Hepatology* disclosed some of the mechanisms responsible for the gender-dependent differences observed in experimental models of intestinal inflammation. In their current work, Goodman et al[6] showed that genetic silencing of the estrogen receptor-α (ERα) in female mice resulted in protection from chemical-induced intestinal inflammation (dextran sodium sulfate [DSS]). On the contrary, this gender difference was reversed in the case of ERβ knockout mice because DSS-treated ERβ-deficient female mice showed increased signs of intestinal inflammation compared with male mice.[6]

Biological effects of estrogens are mediated by at least 2 related members of the steroid-receptor superfamily: ERα and ERβ. ERα and ERβ are nuclear receptors that homodimerize and translocate to the nucleus after ligand binding, and regulate transcription of target genes through either binding to estrogen-response elements in the DNA or by tethering to and influencing the functions of other transcription factors.[7] The nature of the ER interactome not only will determine the distinct role of ERs in a specific tissue, but also will determine different roles of the same receptor in different tissues. In this way, ERs can modulate several physiological and biological processes ranging from lipid and glucose homeostasis cell proliferation and growth, to immunity, reproduction, and brain development.[7] Thus, it is not surprising that defective ER signaling has been linked to a variety of diseases such as cancer, metabolic and cardiovascular disease, neurodegeneration, inflammation, and osteoporosis.[7]

Goodman et al[6] investigated if sex-specific differences in ERα or ERβ gene expression may underlie differences in male vs female responses to DSS treatment. However, knockout of each individual ER isoform results in compensatory up-regulation of the other receptor, both in male and female mice, making it unlikely to contribute to sex-based differences.[6] ERα and ERβ gene expression also was comparable between male and female UC colon samples, suggesting that sex-based differences in ER-mediated effects are most likely not caused by differences in gene expression. It is possible that despite equivalent gene expression, protein expression of ERα/ERβ may be different in males and females, as has been previously shown in the case of colon cancer tissues.[8] Alternatively, the signaling downstream of ERα/ERβ may results in differential patterns of gene expression in males and females, ultimately leading to enhanced colitis in males. Analysis of gene expression from inflamed colonic tissues identified alteration of typical estrogen-responsive genes such as *Socs3*, *Ctsd*, and *Fos* as being up-regulated in colon tissues of DSS-treated ERα-knockout male mice compared with ERα-knockout females. In line with these data, similar gene expression profiles of *Socs3*, *Ctsd*, and *Fos* were found in colonic biopsy specimens from male and female patients suffering from UC.

Overall, these data support the idea that in case of epithelial damage as in DSS colitis and UC, ERβ engagement may result in protection in female mice, but not in males. Interestingly, in a previous study, Goodman et al had shown that male mice but not females were protected by ERβ signaling in an experimental model of Crohn's-like ileitis.[9] This discrepancy may explain an important connection between sex-specific risk to develop UC or CD and protective functions of ERβ signaling in men and women.

ERβ is expressed abundantly in the colonic epithelium, where it has an established role in maintaining colonic architecture, tight-junction formation, and barrier function.[10,11] Notably, ERβ expression was markedly decreased in colonic mucosa of CD/UC patients with active disease,[12] pointing to ERβ as a critical regulator of colonic architecture and function. Importantly, ERβ functions as a dominant-negative regulator of ERα functions.[13] Therefore, ERβ's protective role in the colon may be owing to direct targets of ERβ-mediated gene transcription, or via indirect effects on the inhibition of ERα-mediated targets. However, a clear understanding of the molecular mechanisms by which ERβ signaling protects female colonic mucosa while it worsens intestinal inflammation in males still is missing.

So far, there is no actual cure for IBD, making patients dependent on lifelong symptomatic medical treatment aimed to reduce and/or delay recurrence of intestinal inflammation. Managing IBD is therefore an important priority in gastroenterology, requiring a multidisciplinary approach that combines the optimization of current symptomatic therapies with the development of novel treatments to ultimately cure this devastating disease. Targeting of ER may be a novel approach to IBD treatment during the acute phase of inflammation. Further understanding of the different molecular and cellular mechanisms involved in the gender response and in the engagement of the 2 ER receptors during intestinal inflammation will be of vital importance to improve gender-specific treatment for patients suffering from IBD.

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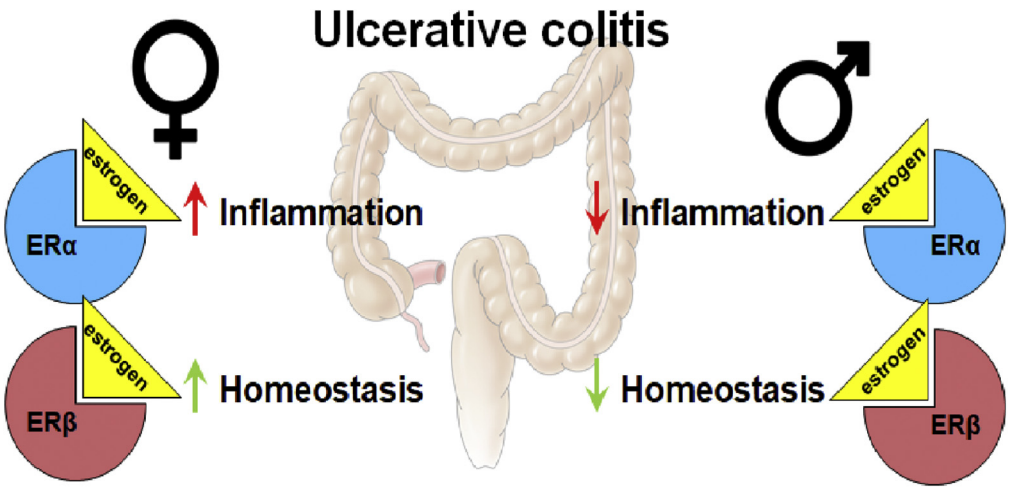

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