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EDITORIAL

Another Breach in the Wall: Impaired Epithelial DUOX2 Activity Fuels Metabolic Syndrome

Metabolic syndrome, characterized by obesity, hyperlipidemia, insulin resistance, and hypertension, has reached epidemic proportions over the past 4 decades, affecting over a billion people worldwide.[1,2] A key role of the gut microbiota has been demonstrated in mouse models using oral antibiotics or microbiota transfer,[3] which resulted in altered metabolic phenotypes. Moreover, breakdown in the integrity of the intestinal barrier has emerged as an important player in the development of the metabolic syndrome due to the leakage of immunostimulatory microbial ligands that can trigger low-grade inflammation locally[4] as well as systemically.[3]

One evolutionary conserved innate defense mechanism in the mammalian gut epithelium relies on the release of hydrogen peroxide upon microbial stimulation.[5] This response is mediated by the heterodimeric dual oxidase 2 (DUOX2) isoenzyme, which consists of DUOX2 and its maturation factor, DUOXA2.[6] Previous work has associated loss of function variants in DUOX2 with various diseases, including congenital hypothyroidism[7] and inflammatory bowel disease.[8–10] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Hazime et al[11] define the role of DUOX2 in driving metabolic syndrome. The authors suggest that the leaky epithelial barrier caused by loss of DUOX2 activity results in bacterial translocation, which triggers adipose tissue inflammation, lipid accumulation, and glucose intolerance, ultimately promoting progression toward metabolic syndrome.

The authors nicely demonstrate that male mice carrying an intestinal epithelial cell–specific deletion of DUOXA1/2 (DA IEC-KO) exhibit progressive weight gain, increased adiposity, and liver hypertrophy when fed a standard chow diet. Compared with wild-type littermates, male DA IEC-KO mice also showed impaired glucose tolerance following oral glucose administration. Plasma markers associated with the metabolic syndrome, including triglycerides, plasma lipoproteins, and very low-density lipoproteins, were all found elevated in males but not in females. This was accompanied by lipid accumulation in the liver and upregulation of genes under the control of the glucose-responsive transcription factor ChREBP, a critical metabolic hub, which transcriptionally controls glycolysis and de novo lipogenesis.[12] Furthermore, male but not female DA IEC-KO mice showed macrophage infiltration in white adipose tissue with increased plasma levels of liver enzymes and of the acute phase protein serum amyloid A1, pointing again to sex-dependent low-grade inflammation in absence of intestinal epithelial DUOX2 activity.

How does loss of epithelial DUOX2 activity ultimately disrupt lipid and glucose metabolism and, more broadly, contribute to the development of systemic low-grade inflammation in males? First, the authors investigated the underlying mechanisms in the colonic epithelium. As expected, colonic intestinal epithelial cells isolated from DA IEC-KO mice exhibited reduced hydrogen peroxide production. However, there was no significant change in the overall colonic mucosal architecture in DA IEC-KO animals, nor any detectable increase in proinflammatory markers, or neutrophils, ruling out local inflammation at the steady state. Yet, male DA IEC-KO mice showed enhanced absorption of orally administered dextran-FITC, indicating increased gut permeability. In keeping with this finding, enhanced lipopolysaccharide and bacterial translocation were observed distally into the liver and the subcutaneous white adipose tissue of male DA IEC-KO mice. Interestingly, barrier integrity was not affected in female DA IEC-KO mice, providing an explanation for their lack of metabolic syndrome phenotype. Compared with wild-type littermates, male DA IEC-KO mice also showed changes in their microbiota with enrichment in Lachnospiraceae and depletion in Akkermansiaceae, a finding that may be compared with data supporting a protective effect of Akkermansiaceae, and notably of *Akkermansia muciniphila*, against metabolic syndrome both in mice and in humans.[13–15] In male DA IEC-KO mice, obesity and metabolic syndrome phenotypes could be rescued by depleting the microbiota through oral antibiotic treatment.

Thus, a healthy microbiome is critical to maintain restricted gut permeability, which in turn prevents systemic low-grade inflammation and avoids metabolic dysfunction. Yet, how dysbiosis induced by loss of DUOX2 activity directly breaches the intestinal barrier remains to be defined. Overall, the findings reported by Hazime et al[11] align with previous studies demonstrating that modulation of the microbiota through other "bricks" of the epithelial wall, such as Toll-like receptor 5[16] or intestinal alkaline phosphatase,[17] prevents the development of metabolic syndrome. Yet, in contrast to these studies, DA IEC-KO mice exhibit a pronounced sex-specific phenotype with a striking absence of metabolic syndrome features in female mice. Increased prevalence of glucose intolerance has been observed in males both in human studies[18] and in mice.[19] A recent study further ascribes sexual dimorphism in glucose metabolism to androgen modulation of the gut microbiota.[20] Accordingly, transfer of male microbiota into antibiotic-treated female mice impaired glucose tolerance and insulin sensitivity.[20] Investigating the microbiome composition in female DA IEC-KO mice will therefore be necessary to explore the sex-specific difference reported by Hazime et al,[11] notably when considering microbiota manipulation strategies. Finally, because rare loss-of-function variants in DUOX2 are associated with predisposition to inflammatory

bowel diseases,[8–10] it would be worthwhile to screen these carrier individuals for metabolic syndrome features in order to translate the findings of Hazime et al[11] to a human context and to advance our understanding of the intricate host-microbiota interplay underlining inflammatory bowel diseases and metabolic syndrome.

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