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EDITORIAL

Neonatal Colonic Inflammation: An Epigenetic Trigger of Adult Disease

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Zhong et al[1] reported that colonic inflammation induced in neonatal rats by intrarectal administration of trinitrochlorobenzene (TNBS) results in more severe colitis after TNBS administration 6–8 weeks later (relative to rats that did not experience neonatal TNBS colitis). They thus concluded that during early life the organism can be imprinted to mount exaggerated inflammatory responses, which persists for a relatively long period of time.

Studies to analyze the basis of the imprinting showed that neonatal rats with gut inflammation released norepinephrine/epinephrine into the circulation and the latter caused epigenetic changes in the interleukin 1β promoter (and perhaps other promoters). These changes, characterized by increased acetylation of histone H4K12, led to increased accessibility of the interleukin 1β promoter to binding of RelA, a nuclear factor-κB component that promotes gene transcription. The investigators thus suggested that substances that are part of the stress response (eg, norepinephrine or epinephrine) caused by the neonatal inflammation induce long-term hyperactivity of proinflammatory genes that, in turn, increase inflammatory responses when the animal is again exposed to factors inducing inflammation (in this case a second exposure to TNBS). The results are striking, but do leave important questions unanswered. For example, how long do the epigenetic changes persist and are norepinephrine or epinephrine the only factors capable of inducing these changes?

The clinical implications of these findings, that gut inflammation occurring early in life can be a risk factor for inflammation occurring much later, are important. Nevertheless, it is not entirely clear how they relate to human disease. Although inflammatory bowel disease (IBD) can occur early in life as a persistent illness, enterocolitis has not been reported as a harbinger of severe IBD when occurring as an isolated incident during childhood, as might be predicted by these studies. Similarly, although there are some reports suggesting that infection of the gastrointestinal (GI) tract in early life occurs with a higher frequency in IBD patients, these reports, taken together, have not established a clear etiologic role for early infection in IBD pathogenesis. Along these lines there is no credible evidence that measles virus infection or live (attenuated) virus vaccination early in life is a precursor of IBD.[2,3]

Although no clinical data support early effects of inflammation on subsequent IBD development, it remains possible that interactions of the neonatal immune system with microbes in the neonatal GI tract do influence susceptibility to IBD or chronic inflammation of other organs, such as the lungs in asthma. Evidence supporting this idea has come from studies showing that germ-free mice develop increased numbers of natural killer T (NKT) cells in their colons that, in turn, results in more severe ulcerative colitis–like inflammation when these mice are colonized by conventional microflora and challenged with intrarectal oxazolone (oxazolone colitis).[4] This increased intestinal inflammation could be prevented by colonization of germ-free neonatal, but not germ-free adult, mice with conventional gut microbiota. Thus, the neonatal immune system provides a window of opportunity during which the propensity to increased gut inflammation can be reversed. Additional studies have indicated that increased secretion of CXC motif chemokine with Ligand 16 (CXCL16) drives NKT cell chemotaxis to, and accumulation in, colonic tissues. Increased CXCL16 secretion was caused by cells with epigenetic changes that increased CXCL16 gene transcription in the germ-free gut. Interestingly, NKT cell expansion in germ-free mice could be reversed in neonatal, but not adult, germ-free mice by colonization with *Bacteroides fragilis* organisms expressing a particular glycosphingolipid, termed Bf717.[5]

The older data relating to NKT cells and oxazolone colitis are similar to the present study of neonatal and recurrent TNBS colitis in that both were driven by persistent genetic changes induced in the neonatal period. Zhong et al[1] point to a number of studies providing evidence that components of the genome are uniquely susceptible to epigenetic changes, such as DNA methylation and histone acetylation, in neonates. These changes can have long-term effects on gene expression that lead to the development of a variety of diseases, including diseases of the GI tract.[6] Determination of whether this is an important influence on IBD development awaits further work.

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Conflicts of interest
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