Proinflammatory enzyme soluble epoxide hydrolase bridges obesity to colonic inflammation and potential carcinogenesis

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Soluble Epoxide Hydrolase: A Mechanistic Link Between Obesity and Colonic Inflammation

Obesity and chronic inflammation are two well-recognized risk factors for the development of colorectal cancer (CRC). In PNAS, Wang et al. (1) use lipidomic profiling analysis to identify a significant mechanistic link between obesity and colonic inflammation via enhancing the proinflammatory enzyme soluble epoxide hydrolase (sEH).

The Potential Role of Soluble Epoxide Hydrolase in Obesity-Promoted Colorectal Carcinogenesis

The aberrant metabolism of polyunsaturated fatty acids, and particularly arachidonic acid, is thought to be a key inflammatory mediator contributing to colorectal carcinogenesis. The role of cytochrome P450 epoxygenase in this metabolism, though, and the role of its epoxy fatty acid metabolites in obesity and CRC are not well known. Endogenous epoxide fatty acid(s) have highly polarized oxygen–carbon bonds, making them crucial signaling molecules/metabolites. It is well known that these epoxy fatty acids have antiinflammatory effects, but physiologically epoxide fatty acid metabolites are quickly inactivated by sEH. As such, sEH is considered a proinflammatory enzyme.

Wang et al. (1) sequentially demonstrate that (*i*) there is an increased expression of sEH and its eicosanoid metabolites in the colons of high-fat-diet-induced obese mice and (*ii*) the knockout or inhibition of sEH ablates obesity-induced colonic inflammation and decreases obesity-induced activation of Wnt signaling. This study raises interest in further investigating whether the ablation of obesity-induced colonic inflammation by sEH knockout or inhibition may lead to inhibition of obesity-promoted colorectal carcinogenesis (2, 3).

Counterbalancing Nonsteroidal Antiinflammatory Drugs-Related Adverse Effects via Targeting Soluble Epoxide Hydrolase

Thus far, nonsteroidal antiinflammatory drugs (NSAIDs) and Cyclooxygenase 2 (COX-2) inhibitor (coxibs) have been the most promising agents for the prevention of CRC (4). However, the side-effect profile and risk of adverse events including gastrointestinal bleeding and cardiovascular events frequently prohibit their widespread clinical use (5, 6). The cardiovascular risks associated with coxibs are due to an imbalance in the production of prostacyclin I_2 (PGI_2, platelet aggregation inhibitor) and thromboxane A_2 (TXA_2, platelet activator) and the accumulation of 20-hydroxyeicosatetraenoic acids (20-HETE, a vasoconstrictor), which increase arterial blood pressure (4, 6, 7). The adverse events of NSAIDs/coxibs may be counterbalanced by epoxyeicosanoid metabolites such as epoxyeicosatrienoic acids (EETs) (7). EETs are known to attenuate inflammation and hypertension and to enhance wound/ulcer healing by (*i*) suppressing cytokine-induced vascular cell adhesion molecules and chemokine-induced chemotaxis (8–10), (*ii*) reducing TXA_2 and 20-HETE-mediated platelet aggregation (7, 11, 12), (*iii*) reducing blood pressure (13), and (*iv*) inhibiting inflammation and enhancing angiogenesis for wound healing (14–16). Therefore, cotargeting sEH and COX-2 to manipulate eicosanoid metabolites has the high potential to synergistically enhance the inhibition of obesity-promoted inflammation and carcinogenesis while also reducing the adverse effects of coxibs and NSAIDs.

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