5-Methoxytryptophan in Systemic Inflammation (p 222)

Wang et al suggest 5-methoxytryptophan has potential as a treatment for systemic inflammation.

Uncontrolled systemic inflammation, such as that which occurs during sepsis can lead to extensive tissue and organ injury and dysfunction, which commonly results in multiple organ failure and death. Few clinical options, besides antibiotics and fluid administration, are available to treat sepsis, but now a discovery by Wang and colleagues may offer new hope. They have identified—5-methoxytryptophan (5-MTP), a metabolite secreted from endothelial cells that acts as an endothelium-protecting, anti-inflammatory molecule. They found that although bacterial lipopolysaccharide (LPS)—a major trigger of the excessive immune response in sepsis—suppressed 5-MTP production in cell culture and mice, provision of exogenous 5-MTP could prevent LPS-induced injury. Indeed, while LPS treatment alone resulted in 65% mortality in mice, there was only 20% mortality in mice treated with LPS. Moreover, in a model of sepsis induced by cecal puncture mice treated with 5-MTP showed significantly increased survival. The team also found that levels of 5-MTP were significantly reduced in patients with sepsis, suggesting that the metabolite might act as both a biomarker as well as a potential new treatment for sepsis.

ANP and Endothelial cGMP/cAMP Cross Talk (p 237)

ANP enhances inflammation of the heart after myocardial infarction, report Chen et al.

Following acute myocardial infarction (AMI), inflammatory cells migrate to the injured heart to remove dead cells and promote tissue recovery. During this time, myocardial expression of atrial and B-type natriuretic peptide (ANP and BNP) is also increases. These peptides are believed to exert a number of cardioprotective effects, including the strengthening of endothelial barrier function to reduce excessive inflammatory cell infiltration and damage. To examine this potential barrier-boosting effect, Chen and colleagues studied mice whose endothelial cells lacked the ANP/BNP receptor, GCA. Surprisingly, they found that these mice had less myocardial damage after AMI, which was associated with a decrease in the number of neutrophils infiltrating the injured heart. Their in vitro studies showed that while in resting endothelial cells ANP treatment increased submembrane cAMP levels, which in turn boosted barrier function, in endothelium subjected to infarction signals—such as TNF-α—ANP treatment actually decreased submembrane cAMP and thus barrier integrity. Increased expression of the enzyme PDE2A in the TNF-α-treated cells was shown to switch the ANP signaling effects, the team found, suggesting that inhibition of PDE2A in the post AMI period might benefit heart repair.

COMP Inhibits Atherosclerotic Calcification (p 261)

COMP-deficiency switches macrophage fate to drive atherosclerotic calcification, say Fu et al.

Vascular calcification is a risk factor for cardiovascular disease and mortality, and calcification of atherosclerotic lesions, in particular, is a robust predictor of acute cardiovascular events. Lesion calcification is mediated by two major cell types of atherosclerotic plaques—macrophages and vascular smooth muscle cells (VSMCs), but even though VSMCs have been shown to adopt an osteogenic (calcifying) phenotype, the role of macrophages is less clear. Cartilage oligomeric matrix protein (COMP) prevents transdifferentiation of VSMCs to an osteogenic fate, and Fu and colleagues now show that the protein has a similar effect on macrophages. They found that in atherosclerosis-prone mice, replacing bone marrow cells with COMP-deficient ones caused the development of more extensive plaques. Furthermore, expression profiling of COMP-deficient macrophages showed these cells had increased expression of genes involved in osteogenesis and in the conversion of macrophages to a proinflammatory (M1) phenotype. The team went on to show that COMP prevents this osteogenic and inflammatory phenotype via interaction with cell surface receptor integrin β3. Indeed, blocking the COMP-β3 interaction could recapitulate the osteogenic and inflammatory macrophage phenotype. Promotion of the COMP-β3 interaction could thus be a therapeutic strategy to limit plaque calcification and rupture, suggest the authors.