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This Month in *AJP*

Intestinal Ischemia-Reperfusion–Induced Inflammation in Humans

Intestinal ischemia-reperfusion (I/R), the restriction and return of the blood supply, of the intestine is a common pathological side effect of surgery that leads to intestinal barrier loss and systemic inflammation. Although intestinal I/R has been frequently studied in animal models, little is known about the inflammatory sequelae of intestinal I/R in humans. Using a human intestinal I/R model, Grootjans et al (Am J Pathol 2010, 176:2283–2291) demonstrated that intestinal ischemia in humans results in intracellular leakage. In addition, I/R-damaged intestinal tissue induced complement activation and increased production of inflammatory cytokines as well as increased expression of intracellular adhesion molecule 1, which led to a heightened neutrophil influx. These data provide the basis for the development of future preventative and therapeutic strategies to treat I/R.

Caveolin-1 Modulation of Endothelial Nitric Oxide Synthase Activity Regulates Innate Immunity and Sepsis-Induced Lung Injury

Nitric oxide plays a key role in innate immunity and inflammation, as does caveolin-1, a scaffolding protein found in caveolae. The caveolin-1/endothelial nitric oxide synthase (eNOS) interaction is thought to be involved in this process. To determine the respective roles of caveolin-1 and eNOS in innate immunity and inflammation, Mirza et al (Am J Pathol 2010, 176:2344–2351) generated mice that were deficient in both *CAV1* and *NOS3*. They show that eNOS activation has an immunomodulatory effect in caveolin-1–deficient mice, resulting in a decrease in the levels of proinflammatory cytokines and improved survival when compared with mice deficient in both caveolin-1 and eNOS. In addition, eNOS activation in caveolin-1–deficient mice protected against lipopolysaccharide-induced lung injury. The interaction between caveolin-1 and eNOS may therefore represent a new therapeutic target for inflammation and lung injury.

Isolated Lymphoid Follicle Development in the Intestine

Isolated lymphoid follicles (ILFs), which can serve as sites for T cell-dependent and -independent IgA production, are instrumental in the intestinal immune response against luminal pathogens. Indeed, in a reversible process, environmental stimuli from luminal microbiota induce nascent lymphoid cryptopatches to develop into the more mature ILFs. McDonald et al (Am J Pathol 2010, 176:2367–2377) discovered that intestinal microbiota recruited clusters of dendritic cells to ILFs. Moreover, depletion of dendritic cells resulted in regression of ILFs to reform cryptopatches, and ILF differentiation was dependent on the chemokine CXCL13, which is expressed by ILF dendritic cells. Taken together, these data indicate that dendritic cell recruitment plays a key role in ILF development and function, perhaps through the secretion of CXCL13.

Tumor Exosomes Accelerate Tumor Metastasis via MyD88

Microvessels, or exosomes, secreted from tumor cells can stimulate inflammation, resulting in the expansion of myeloid-derived suppressor cells (MDSCs) and subsequent tumor growth and metastasis. To determine the mechanisms governing this response, Liu et al (Am J Pathol 2010, 176:2490–2499) investigated the role of MyD88, an adaptor protein involved in Toll-like receptor signaling, in the immune response to tumor exosomes. They found that MDSC recruitment and expansion was inhibited in mice pretreated with MyD88-deficient tumor exosomes and that wild-type tumor exosomes caused higher levels of inflammatory cytokine secretion than MyD88-deficient exosomes. Furthermore, lungs of MyD88-deficient mice expressed lower levels of CCL2, a chemokine important in tumor metastasis, than wild-type mice. MyD88 therefore plays a critical role in tumor exosome-mediated MDSC expansion and tumor metastasis.

MicroRNA Dysregulation May Contribute to Melanoma Development

MicroRNAs (miRNAs) are a class of small noncoding RNAs that regulate gene expression. To examine the hypothesis that differential expression of miRNAs may contribute to melanoma development, Chen et al (Am J Pathol 2010, 176:2520–2529) compared levels of miRNA expression between benign nevi and metastatic melanoma. Of the miRNAs examined, 31 were differentially expressed, with miR-193b significantly down-regulated in all melanoma tissues examined. miR-193b overexpression in tumor cells inhibited proliferation as well as down-regulated numerous genes, including the cell cycle regulator cyclin D1 (*CCND1).* Indeed, miR-193b directly repressed *CCND1* by binding to the 3′ untranslated region of *CCND1* RNA. These results suggest that miR-193b dysregulation may contribute to melanoma development by altering cell proliferation.