Alkylating Agents May Cause Pulmonary Hypertension

Limited studies implicate chemotherapeutic agents as a cause of pulmonary veno-occlusive disease (PVOD), which is characterized by progressive obstruction of small pulmonary veins. Ranchoux et al (Am J Pathol 2015, 185:356–371) explored this relationship in cases of chemotherapy-associated PVOD identified in the French pulmonary hypertension network and by systematic literature review. Exposure to alkylating agents, such as cyclophosphamide, occurred in the majority of cases. In animal models, cyclophosphamide induced pulmonary hypertension accompanied by pulmonary venous remodeling characteristic of PVOD. Further, rats pretreated with a cytoprotective agent displayed improved survival and ameliorated pulmonary hypertension severity after cyclophosphamide exposure. Physicians should therefore consider the risks of alkylating agents for pulmonary vascular complications.

FXR Agonist Is Protective in Gut-Liver Axis

Bacterial translocation (BTL) can be detrimental to patients with chronic liver disease. Using a rat model of cholestatic liver injury, Verbeke et al (Am J Pathol 2015, 185:409–419) examined whether BTL is driven by dysfunctional intestinal signaling in farnesoid X-activated receptor (FXR), knockout of which leads to hepatic inflammation and fibrosis, intestinal inflammation and permeability, and eventually BTL. Rats were gavaged with the FXR agonist obeticholic acid for 10 days after bile-duct ligation. Vehicle-treated rats showed decreased FXR pathway expression in the gut as well as increased intestinal permeability, inflammation, and invasion of luminal bacteria. Treatment with obeticholic acid, however, decreased inflammation, normalized permeability in the ileum, and significantly reduced BTL. The protective effect of obeticholic acid supports further consideration in patients with chronic liver disease.

Granulomatous Inflammation Induces Lymphangiogenesis

Using mycobacterial models of granulomatous inflammation, Harding et al (Am J Pathol 2015, 185:432–445) explored the association between granulomatous tissue and lymphangiogenesis. Vascular endothelial growth factor (Vegf)-c was up-regulated in both Bacillus Calmette-Guerin— and Mycobacterium tuberculosis—induced granulomas, accompanied by sprouting of lymphatic vessels and increased lymphatic area. Inhibition of Vegf receptor 3 (Vegfr3) decreased infection-induced lymphangiogenesis and reduced antigen-specific T-cell proliferation. In a model of chronic granulomatous infection, lymphatic remodeling persisted even after reduction in bacteria and infiltrating leukocytes. Thus, granulomatous inflammation induces lymphangiogenesis, encouraging proliferation of mycobacterial-specific T cells.

Novel Regulation of Xylosyltransferase-1 in Nucleus Pulposus Cells

Glycosaminoglycans are critical in regulating the function of nucleus pulposus (NP) cells of the intervertebral disk. Ye et al (Am J Pathol 2015, 185:485–495) investigated the effect of disk degeneration and associated inflammatory cytokines on the expression of the key glycosaminoglycan biosynthetic enzyme xylosyltransferase-1 (XT-1) in human NP tissue and cultured cells. Increased disease severity had no effect on XT-1 expression in human NP tissues. XT-1 levels positively correlated with Jun, Fos, and specificity protein (Sp)1 mRNA levels. Although XyLT1 promoter activity and expression remained unaffected by cytokines, specific promoter alterations decreased activity, implicating activator protein 1 (AP-1), Sp1, and Sp3. Such signaling is critical for maintaining XT-1 levels under physiological and pathophysiologic conditions in NP cells.

Alleviating Ischemic Stress in the Retina

Ischemic retinopathies exhibit robust inflammation leading to generation of IL-1β, vascular degeneration, and impaired retinal revascularization. Using an established mouse model of oxygen-induced retinopathy (OIR) and cultured cells, Sitaras et al (Am J Pathol 2015, 185:581–595) studied the role of proteinase-activated receptor-2 (Par2) in OIR. Par2 was up-regulated in OIR, but Par2-knockout mice exhibited no changes in OIR—induced vaso-obliteration and neovascularization, suggesting compensatory mechanisms. Conditional knock-down of retinal Par2 led to aberrant revascularization, whereas a Par2 agonist accelerated normal revascularization. IL-1β induced Par2 expression in retinal neuronal and endothelial cells and down-regulated expression of interleukin-1 receptor inhibitor and semaphorin 3A, facilitating retinal revascularization. Par2 agonists may be a promising therapeutic avenue in treating ischemic retinopathies.