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CXCL9 contribution to autoimmune arthritis: Synergy between TLR ligands and inflammatory cytokines to produce leukocyte-attracting chemokines

Rheumatoid arthritis is a complex inflammatory disease that involves microvasculature proliferation in the joint. This angiogenic process facilitates the recruitment of leukocytes, which amplify the inflammatory cascade at the site of injury. Chemokines produced by endothelial cells play a key role in leukocyte recruitment to inflamed tissues. Inflammatory cytokines are essential mediators of autoimmune arthritis pathogenesis, as demonstrated by the spectacular success of therapeutic treatments targeting TNFα or IL-1β. One of the functions of these cytokines is to induce chemokine production. Chemokines can also be induced by microbial products binding to Toll-like receptors (TLR). In a paper presented in this issue, **Loos *et al*[1]** (p. 902) have characterized the interactions between inflammatory cytokines and TLR ligands in endothelial cells. Comparison was made between CXCL8 (IL-8), which binds CXCR1 and CXCR2, versus the CXCR3 ligands CXCL9 (Mig), CXCL10 (IP-10), and CXCL11 (I-TAC). In contrast to CXCL8, CXCR3 ligands are not induced in endothelial cells that are only stimulated with microbial products. The combination of IFNγ and specific TLR ligands showed, however, a great synergy in inducing CXCL9, CXCL10, and CXCL11. Peptidoglycan (PGN) and lipopolysaccharide (LPS), bacterial products that bind to TLR2 and TLR4, respectively, synergized with IFNγ to induce CXCL9 and CXCL10. Likewise, dsRNA, a by-product of viral infection that activates TLR3, induced all three CXCR3 ligands. Interestingly, TRL5, TR7, and TRL9 ligands had no effect on the production of these chemokines by endothelial cells. Similar results were obtained when TLR ligands were replaced by IL-1β or TNFα, two cytokines that are located downstream of TLR stimulation. The relevance of these in vitro results was validated by finding a significantly increased expression of CXCL9 but not CXCL11 in the synovial fluid of patients with autoimmune arthritis, but not in nonautoimmune metabolic crystal-induced arthritis. Given that TLR are strategic sensors for bacterial by-products, these data suggest that bacterial infection may play a greater role than viral infection in the amplification of joint autoimmune pathogenesis. More importantly, this work clearly demonstrates a role for the innate immune system and its recognition of microbial products by endothelial cells through TLRs in the pathogenesis of autoimmune arthritis. However, the implications of these results are not limited to arthritis, but also have broad implications for other pathogenic conditions combining inflammation and microbial challenge.

Reference

1 Loos T, Dekeyzer L, Struyf, S *et al*. TLR ligands and cytokines induce CXCR3 ligands in endothelial cells: Enhanced CXCL9 in autoimmune arthritis. Lab Invest 2006;86:902–916.

Culturing up polycystic kidney disease—from the liver

The inherited polycystic diseases are an intriguing assortment of disorders that variably affect the kidneys, liver, and pancreas. Autosomal dominant polycystic kidney disease is an insidious condition in adults in which renal cysts gradually enlarge and eventually obliterate most of the normal renal parenchyma in the adult. Incidental cysts also occur in the liver and pancreas. Autosomal recessive polycystic kidney disease (ARPKD), in contrast, is a devastating disease in the infant. The kidneys become markedly enlarged during gestation, resulting in pulmonary hypoplasia and impaired lung function at birth. By the time of term birth, the two retroperitoneal kidneys fill much of the available space in the abdominal cavity. Those children who do survive the perinatal period develop liver cystic disease, engendering its own morbidity and mortality. The biliary disease is striking. In addition to cyst formation there is biliary dysgenesis in the form of bile duct dilatation and a 'congenital hepatic fibrosis' lesion: dense portal tract fibrosis with residual marginal ductular remnants of the embryonic biliary tree. The pathogenesis of these disorders also is striking, as single gene defects have been identified in the ciliary apparatus of epithelial cells. In the case of ARPKD, the gene defect is in *PKHD1*, which encodes a large transmembrane protein, fibrocystin. It is expressed in the sensory cilia of normal renal and biliary epithelia. Disruption of fibrocystin expression in the 'PCK' rat leads to kidney and liver cystogenesis. Despite the creation of an autosomal recessive animal model, the function of fibrocystin remains unknown. This is due in part to the inability to perform molecular studies on the malformed cilia of the affected epithelial cells. In this issue, **Muff *et al*[1]** (p. 940) report the successful development of a cholangio-

cyte cell line derived from the intrahepatic bile ducts of the PCK rat. In culture, these cells grew twice as fast as normal rat cholangiocytes. When seeded in 3-D cultures, the abnormal cells formed cysts, which expanded progressively, unlike normal rat cholangiocytes whose 3-D cysts remained of stable size after 9 days in culture. Ultrastructurally, the characteristic shortened and abnormal cilia were observed in the fibrocystin-deficient cells. Their sustained growth through 45 passages without undergoing crisis or senescence suggests that the cells become spontaneously immortalized. In keeping with the somatic mutation of the PCK rat, mutated *Pkhd1* was expressed at the mRNA level. Hence, it is highly likely that this novel cell line will be of great value for studies of the molecular pathogenesis of polycystic disease, and for gaining general insights into the structure:function of cilia.

Reference

1 Muff M, Masyuk T, Stroope A, *et al*. Development and characterization of a cholangiocyte cell line from the PCK rat, an animal model of Autosomal Recessive Polycystic Kidney Disease. Lab Invest 2006;86:940–950.