This Month in AJP

(Guest edited by Steven L. Kunkel and Marc Landanyi)

API2-MALT1 Fusion May Identify a Favorable Subset of Pulmonary Mucosa-Associated Lymphoid Tissue (MALT)-Type Lymphoma

The chromosomal translocation (t(11;18)(q21;q21) of MALT lymphoma results in the API2-MALT1 gene fusion but not all MALT lymphomas contain this specific gene rearrangement. Pulmonary MALT lymphomas show a particularly high prevalence of API2-MALT1 positivity. Okabe et al (Am J Pathol 2003, 162:1113–1122) now report that, among pulmonary MALT lymphomas, those containing this fusion gene present with more favorable clinical and histological features. This is in contrast with the relatively unfavorable impact of API2-MALT1 in gastric MALT lymphomas, where it is associated with poor response to Helicobacter pylori eradication. These investigators also show that, as in gastric MALT lymphomas, aberrant nuclear BCL 10 expression is strongly correlated with the presence of the API2-MALT1 gene fusion in pulmonary MALT lymphomas.

Mononuclear Cell-Infiltrate Inhibition by Blocking Macrophage-Derived Chemokine Results in Attenuation of Developing Crescentic Glomerulonephritis

The recruitment of specific leukocyte subpopulations is important to the evolution of the pathology associated with glomerulonephritis; however, only recently have studies demonstrated a mechanistic role for the chemokines in this process. The studies of Garcia et al (Am J Pathol 2003, 162:1061–1073) demonstrate that one chemokine, macrophage-derived chemokine (MDC), plays an important role during the development of inflammation associated with experimental glomerulonephritis. The elicitation of mononuclear phagocytes into the glomeruli, which is a hallmark of many forms of glomerulonephritis and correlates with loss of renal function, was associated with a significant increase in the expression of MDC. Blocking the in vivo function of MDC dramatically blocked mononuclear phagocytic recruitment to the glomeruli and ameliorated renal function impairment normally found in this model. Further studies found that MDC activity was dependent, in part, on a new variant of the MDC receptor, CCR4. These investigations support a role for MDC during the development of glomerular injury and suggest that targeting CCR4 is an important therapeutic option to intervene in the progression of this disease.

Rearrangement of the Peroxisome Proliferator-Activated Receptor γ (PPARγ) Gene Is Linked to More Aggressive Histological Features in Follicular Carcinoma

A minority of follicular thyroid carcinomas contain rearrangements of the PPARγ gene at 3p25, usually resulting in a PAX8-PPARγ gene fusion. French et al (Am J Pathol 2003, 162:1053–1060) show that this subset of follicular carcinomas is more likely to display unfavorable histological features, such as vascular invasion and solid or nested areas. No follicular adenomas and only very few cases among other subtypes of thyroid carcinoma showed evidence of PPARγ rearrangement, confirming the specificity of this genetic marker for follicular carcinomas. They also show that intense nuclear immunoreactivity with anti-PPARγ antibody is specific for the presence of PPARγ rearrangement, thereby providing a high-throughput approach to retrospective analyses of archival series of this uncommon subset of thyroid carcinomas.

Expression and Regulation of Toll-Like Receptor 2 in Rheumatoid Arthritis Synovium

A variety of scientific investigations have identified the family of toll-like receptors (TLR) as important participants in innate immunity, as these cell surface proteins are known to bind microbes and microbial products, leading to inflammatory cell activation. Interestingly, recent investigations have suggested that the expression of TLR is not only restricted to a primary role in innate immunity, but may participate in chronic cell-mediated immune diseases. Seibl et al (Am J Pathol 2003, 162:1221–1227) have identified the expression of TLR2 by synovial fibroblasts treated with IL-1, TNF, LPS, or sBLP (synthetic lipopeptide). Further investigations demonstrated that TLR2 activation by the synovial fibroblasts led to NF-κB translocation, demonstrating the functionality of TLR2 on these fibroblasts. These observations support a role for TLR during the initiation and maintenance of rheumatoid arthritis and suggest that the chronic nature of this disease may be dependent on novel activation pathways such as the TLR.
**Malgun Cells as the Morphological Manifestation of Helicobacter pylori Gastritis-Associated DNA Damage**

*Helicobacter pylori* gastritis is epidemiologically associated with gastric cancer. The mechanism underlying this association is thought to involve prolonged acute foveolitis targeting the proliferative zone of gastric pits. Jang et al (Am J Pathol 2003, 162:1203–1211) report that Malgun cells (as the clear cell change seen in acute foveolitis is described) show evidence of DNA damage and repair, in the form of TUNEL staining for double-strand DNA breaks and the expression of several proteins implicated in these two processes. Their results establish a morphological counterpart for the genotoxic damage that is thought to precede recognizable pre-neoplastic lesions, thereby providing a valuable lead for further work linking the genotoxic effects of persistent acute inflammation to gastric carcinogenesis.

**Potential Interaction between CCR1 and Its Ligand, CCL3, Induced by Endogenously Produced Interleukin-1 in Human Hepatomas**

One of many enigmas of tumor cell biology is the ability of transformed cells to overexpress a variety of cytokine mediators, which are normally associated with inflammatory responses. Lu et al (Am J Pathol 2003, 162:1249–1258) demonstrate that hepatoma tissue, but not normal liver tissue, and hepatoma cell lines overexpress the chemokine CCL3 (MIP-1α) and its receptor CCR1. The CCR1 expressed by the hepatoma cells was functional, as forskolin-mediated increases in intracellular cAMP were suppressed in these cells when the specific chemokine ligands for CCR1 were added. In addition, production of the chemokine by hepatoma cells was mediated via a cytokine network. These cells constitutively generate an abundance of IL-1 that serves as a stimulus for the production of CCL3 in this system. The study extends previous investigations that demonstrated that tumors have the ability to regulate the expression of different immune mediators via an autocrine or paracrine pathway.