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Profiling and cellular localization of metalloproteinases in autoimmune disease

Autoimmune disease is a complex phenomenon resulting from dysregulation of immune system. This involves T and B lymphocytes, which react to a self-protein to mediate tissue dysfunction. The cascade of events leading to autoantibody and autoreactive T-cell formation is incompletely understood. Recently, the role of the extracellular matrix in modulating the migration of immune-specific cell types has garnered attention as being important in the pathogenesis of autoimmune disease. Matrix metalloproteinases (MMPs) are part of the metzincin superfamily of metalloproteinases (MPs), which also includes the metalloproteinase-disintegrins (ADAMs). Their tissue inhibitors (TIMPs) are produced locally, enabling homeostatic matrix regulation. The localization of MPs in autoimmune disease has not been adequately examined.

Toft-Hansen *et al*¹ recently studied the gene expression of MPs (22 MMPs, seven ADAMs, and four TIMPs) in an animal model for multiple sclerosis, experimental autoimmune encephalitis (EAE). Using RT-PCR they found a significant increase (>3-fold) in RNA transcription of MMP-8, MMP-10, MMP-12, MMP-15, ADAM-12, and TIMP-1 in EAE animals at the height of their disease, as compared to the control mice. In addition, there was a significant (>3-fold) downregulation of MMP-15. The comparison of absolute levels of RNA for these genes revealed that only TIMP-1 was expressed at low levels in the control, but became the highest expressed during active disease. Using flow cytometry, immunohistochemistry and *in situ* hybridization, the authors also demonstrated that each of the immune cell types: macrophages, granulocytes, T cells and microglia, often perivascular in location, produced exclusively one or more proteins. These results indicate that inflammatory cells in EAE produce a distinct pattern of MP gene expression, which correlates with the disease course.

Similarly, Ciccocioppo *et al*² in this issue, studied another autoimmune process—celiac disease. They demonstrated elevation of MMP-1, MMP-12, and TIMP-1 RNA levels as well as significantly decreased MMP-2 levels in active disease. They also showed that mononuclear cells in the lamina propria-produced MMPs. Under physiological conditions, MMPs were produced after cytokine stimulation, while during active disease they were constitutively expressed.

Since gene expression of MPs are somewhat similar between active celiac disease and multiple sclerosis, further studies of these genes are warranted to gain additional insight into the pathogenesis of autoimmune diseases. In addition, by comparing the specific differences between the MP profiles of various autoimmune diseases, insight into the specific manifestation of self-recognition may also be gained.

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References

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Pyothorax-associated lymphoma: a distinct variant of diffuse large B-cell lymphomas

Pyothorax-associated lymphoma (PAL) refers to a group of malignant lymphomas developing in the pleural cavity in a clinical setting of long-standing inflammation. PAL resembles diffuse large B-cell lymphoma (DLBCL) histologically, but shows a strong association with Epstein–Barr virus (EBV) infection. The current WHO classification does not list PAL as a distinct variant of DLBCL, partly because it is rare in the Western countries and its genetic profile is unknown. However, it is generally accepted as an entity separate from DLBCL based on its unique clinical presentation. Although the molecular mechanism of PAL oncogenesis is still largely unexplored, the genetic basis of PAL is starting to unfold.

It appears that the genetics of PAL are quite different from DLBCL at the global gene expression level. In a study conducted by Nishiu *et al*¹ using cDNA microarray, researchers found that PAL cell lines or clinical specimens had significantly different expression levels of a large group of genes involving apoptosis, interferon response, and signal transduction, when compared to nodal DLBCL. Among them, the *interferon- α -inducible protein 27* (IFI27) was highly expressed in PAL, as confirmed by RT-PCR, suggesting an important role of the inflammatory response in PAL oncogenesis. In addition, PAL showed increased expression of activated B-cell-like signature genes and distinct gene clustering relative to nodal DLBCL. These results demonstrate that PAL is distinct not only

clinically, but also genetically, from usual nodal DLBCL.

In this issue of the *Lab Invest*, Liu *et al*² studied the genetic alteration of PAL from a different angle. They demonstrated that the majority of PAL cell lines had mutation of the ataxia-telangiectasia mutated (ATM) gene. Approximately half of PAL clinical samples showed mutation of Rad3-related (ATR) genes. ATM/ATR genes maintain genomic stability by functioning in a key cell cycle checkpoint, the G2 phase of the cell cycle in particular, in response to DNA damage and telomeric instability. These genes also participate in the cellular response to oxidative stress. Oxidative stress is commonly associated with the chronic inflammation that activates cytokines and releases free radicals. The ATM gene is specifically implicated in the repair of DNA double-strand breaks caused by free radicals and other insults. In their study, the functional consequence of ATR mutations in the two PAL cell

lines was failure to repair DNA single-strand breaks induced by UV light.

The functional findings of Liu *et al*, together with their gene profiling data and the genetic analysis of PAL by Nishiu *et al*, confirm that PAL is a distinct entity characterized by a unique pattern of global gene alterations and abnormal DNA repair mechanisms.

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References

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