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Issue Highlights for May 2006

Sjögren's syndrome and impaired NK-cell function—how do autoimmunity, immune dysfunction and a tendency to develop lymphoma fit together?

In 1888, Univ. Prof. Dr. Med. Johannes Freiherr von Mikulicz-Radecki presented a paper to the *Königsberger Arztkammer*, describing an unusual syndrome of symmetrical swelling and round-cell infiltration of the lachrymal and salivary glands; a more detailed description was published four years later in *Beiträge zur Chirurgie* (in a special *Festschrift* issue dedicated to the renowned surgeon, Theodor Billroth).[1] In the 1930s, the Swedish ophthalmologist Henrik S.C. Sjögren's noted the association of arthritis and occasionally alopecia with the salivary and lachrymal findings, and recognized the disorder as a systemic illness[2,3] — it now bears his name.

The nature of the immune dysregulation in Sjögren's syndrome is not entirely understood, but it includes failure of immune surveillance, resulting in an increased risk of lymphoid malignancy; a paper in this month's issue of the *Journal* explores natural killer (NK) cell number and activity in patients with Sjögren's Sydrome and compares them to well controls.

Dr. Yasumori Izumi, with colleagues from the Nagasaki University and Harvard Medical School, examined fifteen patients who had recently been diagnosed with primary Sjögren's syndrome, comparing them with sixteen control subjects. They assessed the number of peripheral blood NK cells, NK cell activity against known targets, expression of NK-cell-activating receptors, and serum cytokine levels. As predicted (and agreeing with findings in some other systemic auto-immune disorders), they found that NK cell number and NK cell killing activity were significantly decreased in the Sjögren's patients. Concomitantly, the expression of activating receptors CD2 and NKG2D on NK cells were also decreased. In what may have been a compensatory accommodation, the expression of a different activating receptor — NKp46 — was significantly increased in cells from the Sjögren's patients. Moreover, the percentage of apoptotic NK cells was also increased in patients compared with healthy controls.

When NK cell killing activity was assessed on a per-cell basis, it was not much different between patients and controls, so much of the effect was presumably attributable to apoptosis. Indeed, the levels of IL-18 and TNFα, cytokines that have been shown to promote NK cell death, were increased in sera from patients with primary Sjögren's compared with controls. The authors conclude that

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decreased NK cell numbers, rather than impaired function of individual NK cells, accounts for much of the impaired overall NK cell activity in patients with primary Sjögren's syndrome. This paper appears on page 242.

Glycated proteins and the pathogenesis of diabetic complications—different roles for the Amidori products and the end-stage glycation products

Diabetes is associated with end-organ damage in a number of systems; it is the leading cause of renal failure, a leading cause of loss of vision and a leading cause of peripheral neuropathy in the U.S.; it also carries a several-fold increase in the risk of myocardial infarction and a several-fold increase in the risk of limb amputation for peripheral vascular disease.

Just why is diabetes so tough on the vasculature? A lot of evidence in the past three decades has implicated glycated proteins. Practicing physicians are familiar with the fact that reducing sugars may condense (non-enzymatically) with susceptible amino groups, at a rate that is higher in the presence of hyperglycemia; that is the basis of a common clinical test: the measurement of glycated hemoglobin as a rough measure of the average level of glucose in the blood. But hemoglobin isn't the only protein to gain carbohydrate when chronically exposed to sugar, and the acquisition of carbohydrate may have implications for the function and kinetic fate of the glycated protein.

Recently, interest has centered on the existence of several stages in the glycation of long-lived proteins, ranging from early single condensations to "advanced glycation endproducts," the latter including multiple glycations, oxidation products and other secondary changes. While both may be important in the pathogenesis of diabetic complications, the early "Amadori-modified" products may work in distinct ways (and certainly via different receptors) from those of the more extensively modified proteins. *Dr. Margo P. Cohen* this month provides a review of recent information in this field, with special attention to the pro-atherotic effects of the Amadori products (see page 211).

Do tumor-suppressor genes play a role in benign pulmonary disease?

Chronic obstructive pulmonary disease (COPD) is a common disorder, highly associated with cigarette smoking. It results at least in part from disruption of the normal balance between proteases and antiproteases. That is, tobacco smoke recruits inflammatory cells (and their proteases) to the lung, while it also (through oxidants) inactivates the antiproteases that would normally protect the lung from autodigestion. There is wide variability in the susceptibility to smoking-induced lung injury.

Smoking tobacco is also a leading cause of malignancy of the respiratory tract, with several mechanisms available to invoke—including benzene delivery, oxidant stress, and a wide assortment of carcinogenic substances in tobacco smoke and its tarry residue. There is also an apparent wide range in susceptibility to smoking-associated oncogenesis.

Might these two be related at the molecular level? If one tested for tumor risk genes in patients with chronic obstructive airways disease, would one find abnormalities similar to those one finds in malignancy? That's what was done by a group of researchers at the Chung Shan Medical University and the National Taiwan Normal University, whose results appear beginning on page 228 of this month's issue.

Two hundred and six smokers with chronic obstructive lung disease were compared with 210 smokers without obstructive disease. DNA was extracted from the subjects' peripheral blood lymphocytes, and mutations in *p53* and *p21*—two known tumor-suppressor genes—were sought by polymerase chain reaction. The researchers found that the distribution frequencies of genotypes of *p53* codon 72 and *p21* codon 31 were significantly different between the COPD and control groups. COPD was more likely to be present in individuals with p53 Pro/Pro or Pro/Arg genotypes than in