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INSIDE LAB INVEST

THE BEGINNINGS OF STEM CELL PATHOLOGY: In recent years biomedical research has benefited from addressing questions at the cell biological and molecular levels of organization. Organismal models have yielded much relevant information as well, but the understanding of functional pathology at the tissue level has lagged behind. Tissue physiopathology has largely been tissue histopathology. Studies such as the one appearing in this issue by **Kosugi et al** (Lab Invest 2000;80:1373-1383) explore the role played by tissue development and organization in the pathogenesis of disease. It seems that the crucial factor explaining the morphology of the neonatal central nervous system (CNS) lesions caused by cytomegalovirus (CMV), is the infection of CNS stem cells. Murine CNS stem cells are less permissive for CMV than murine fibroblasts, but infection of the former not only inhibits proliferation but also modifies their response to differentiating agents. In vitro experiments by Kosugi and co-workers demonstrate that the neuronal differentiation of stem cells caused by epidermal growth factor (EGF) is inhibited when the cells are infected by murine CMV. When infected CNS stem cells are transplanted into neonatal rat brains, they fail to proliferate and fail to migrate and differentiate. Thus, the work of Kosugi et al suggests that the study of pathological processes specifically affecting the stem cells will illuminate poorly understood areas of developmental and cancer pathology. Tissular lesions may be the consequence of disruption of the stem cell charged with the maintenance of functional and architectural tissue integrity.

NO AND CELL-MEDIATED IMMUNITY TO MYCOBACTERIA: Cell-mediated immunity against infectious organisms was first clearly defined in experiments that showed that lymphocytes (now known to be T cells), but not antibodies from immunized mice, could transfer protective immunity to naïve mice. Subsequent in vitro experiments showed that the lymphocytes did not directly kill the microbes but rather, in response to microbial antigens, would activate macrophages to do so. T cells can activate the microbicidal functions of macrophages by releasing cytokines, such as interferon-γ (IFN-γ) and TNF, or by contact-dependent signals such as those delivered by CD40 ligand on the T cell binding to CD40 on the macrophage. The macrophage responds to these signals by synthesizing new proteins, such as the phagocyte oxidase complex, which generates reactive oxygen intermediates. In mice, and probably in humans as well, a second microbial system is mediated by the inducible high-output form of nitric oxide synthase (NOS), referred to as i-NOS or NOS-2. The biology of nitric oxide (NO) is complex because it can be made by several different cell types using several different isoforms of NOS and because, in addition to its role as a toxin, NO also delivers signals to cells and modifies the signals produced by other inflammatory mediators. Dissecting out these functions of NO is difficult in wild-type animals, and many investigators have turned to NOS knockout mice that are lacking in one or more isoforms of this enzyme to clarify matters. In the present issue of the journal (Lab Invest 2000;80:1385-1397), **Garcia and colleagues** use NOS-2 knockout mice to evaluate the cell-mediated immune response to infection with the BCG mycobacterial strain (*M. bovis* BCG). The striking finding is that NOS-2 deficient animals make granulomas, but they cannot control the infection. The granulomas are actually larger and show more extensive necrosis than those formed in wild-type mice. More TNF is released, but so are the TNF receptors, which effectively block the action of this cytokine. IFN-γ production is diminished, suggesting that the T cell response is also ineffective. While these findings are clear in this model, they are not universal. Indeed, prior reports have shown that NOS-2 knockout mice are perfectly able to handle *M. avium*, another mycobacterial species. These contradictions highlight the need for more detailed studies in patients infected with mycobacteria if new therapies are to be developed for dealing with the growing mycobacterial pandemic.

INSULIN-DRIVEN HEPATIC CARCINOMA—ALL IN THE FAMILY: The ability of autocrine and paracrine growth factors, and receptor oncogenes, to promote carcinogenesis is deceptively simple because growth factors and receptors usually have several protein relatives with overlapping functions. In this issue the report from **Scharf, Ramadori, and Dombrowski** surveys changes that affect an entire hormone/receptor suite during progressive stages of liver carcinogenesis (Lab Invest 2000;80:1399-1411). In the rat model used, hyperinsulinemia is induced in portions of the liver by implantation of pancreatic islet cells in the portal circulation. Insulin, insulin-like growth factor I (IGF-I), and insulin-like growth factor II, regulate cellular processes by binding to insulin receptor (IR), insulin-like growth factor receptor I (IGF-1R), and IGF-II R. The latter governs protein routing to lysosomes and may be a human tumor suppressor. IR and IGF-1R are most strongly associated with metabolic responses (IR) and growth regulatory responses (proliferation and survival; IGF-1R). Actions of insulin family hormones are further modulated by binding to IGF binding proteins (IGF-BPs), which can have either negative or positive influences on receptor activation. IGF-1, IGFBP-4, IGF-II R, were elevated in early preneoplastic lesions. IGF1-R, which is sparse in normal liver tissue, was overexpressed in carcinoma, sometimes in concert with IGF-II. Hence, the initial insulin response may be augmented by increased local production of IGF1, and by IGFBP-4 serving in a positive regulatory role. A shift from high mitogenesis, offset by high apoptosis in intermediary stages, to rapid clonal growth later may be caused by increased production of the IGF-1 receptor, which would channel more of the growth factor response to this strongly anti-apoptotic, pro-mitogenic receptor, rather than to the IR. The importance of sequential changes in ligand/binding protein production and receptor deployment is likely to extend to the several growth factor/receptor signaling families that have been linked to human cancer.

X-LINKED INHIBITOR OF APOPTOSIS IN SJÖGREN'S SYNDROME: Sjögren's syndrome (SS) is a classic autoimmune disorder characterized by lymphocytic and plasma cell infiltration of the lacrimal and salivary glands, with destruction of the acini and ducts and end-stage fibrosis. Beyond the mysteries surrounding the genesis of the autoimmune reaction itself, the mechanisms that effect acinar/ductal cell destruction are poorly understood. In other tissues, part of the answer appears to lie in the control of epithelial cell apoptosis, regulated by both intrinsic and extrinsic factors. In this issue (Lab Invest 2000;80:1421-1427), **Nakamura et al** demonstrate for the first time that this principle is also at play in SS, but with an interesting twist. Using immunohistochemical techniques, they demonstrate that, whereas the common anti-apoptotic molecules Bcl-2 and Bcl-X are expressed in the salivary glands of patients with SS, their expression is confined to the infiltrating lymphocytes, not the epithelial cells. Conversely, in the ductal and acinar cells themselves, the key regulator of apoptosis is a protein derived from the X chromosome, X-linked inhibitor of apoptosis (XIAP). Using an in vitro model system, they demonstrate that in salivary gland cells XIAP is up-regulated by several cytokines (IL-1β, TGF-β1, and IL-10), and surprisingly, is down-regulated by TNF-α, the source of which is the infiltrating leukocytes. Collectively, these results suggest the novel hypothesis that cytokines, expressed in situ in the salivary glands of patients with SS, modulate secretory function by regulating apoptosis and that XIAP is an important target of this process. It follows that a large measure of the pathology characteristic of this disorder (gland destruction) might directly result from the inappropriate activation of apoptosis by the TNF-α released from the infiltrating leukocytes. Unanswered is why 90% of afflicted patients are women (might one not expect the opposite?); the role of other important modulators of apoptosis, such as cIAP1, cIAP2, and survivin; and whether this new information will be useful in future therapeutic approaches that might seek to interdict this pathway.