

INSIDE LAB INVEST

ONE MORE ASSET IN THE MARCH TOWARD PREDICTIVE PATHOLOGY: It is to be expected that expanding the modalities pathologists can use to interrogate tissues will increase the predictive power of histopathology. The advent of comprehensive genomics and proteomics technologies has already demonstrated that prognosis and response to therapy can be determined from the patterns of gene expression or proteomic profiles obtained from tissue samples. An obvious limitation of this strategy, grinding up a tissue sample in order to analyze it, is that the different components of a lesion are merged, and, as a result, the patterns one observes represent a blend of the many individual entities making up the lesion. In tumors we deal with different classes of tumor cells, different types of mesenchymal cells composing the “supporting stroma,” plus wandering cells, eg, lymphocytes, mast cells, and macrophages that infiltrate the tissue. Given this complexity, it is surprising that the profiles obtained are revealing of the basic biological properties of the lesions examined. To overcome these limitations pathologists have deployed two tactics: micro-dissection coupled to amplification and in-situ analysis in a multiplex mode. Both approaches have their respective Achilles’ heels (eg, we do not know how to amplify proteins!), but the in situ mode, provided that one can examine multiple entities simultaneously on the same section, is attractive for the obvious reasons. Inside this issue, **Kitayama et al** present intriguing results obtained by analyzing the numerical centromeric abnormalities of 18 chromosomes that can be found in gastric carcinoma (Lab Invest 2003, 83: 1311–1320). Not only did they find differences according to histo-type, but the authors also uncovered a dramatic difference in outcome predicted by numerical abnormalities present in a subset of the chromosomes examined. One can easily imagine that this strategy coupled to protein interrogation with antibodies is likely to yield effective ways to shift to personalized and predictive pathology!

FUNCTIONAL REGULATION OF IL-12 PRODUCTION BY PHAGOCYTES DURING SEPSIS: Severe sepsis is a syndrome of disseminated infection with end-organ dysfunction. If unresolved, progression to shock and death frequently ensues. Current concepts of sepsis pathogenesis emphasize the concept that end-organ damage and shock result from the uncontrolled, intravascular release of host-derived proinflammatory mediators. Paradoxically, there also is evidence for deficits in certain cell responses during sepsis, which suggests that a more complex state of immune dysregulation exists. In this issue, **Ethuin et al** examine the potential role in severe sepsis of two isoforms of IL-12, which is a phagocyte-derived cytokine that promotes interferon- γ production, enhances natural killer cell activity, and induces T_H1 T cell differentiation (Lab Invest 2003, 83: 1353–1360). IL-12 is a 70 kD heterodimer composed of two disulfide-bound subunits, designated p35 and p40. Of note, the p40 subunit also is secreted as a monomer or a homodimer, and it is thought to be a natural antagonist to the IL-12 heterodimer by competitive binding to the IL-12 receptor. The authors show that an imbalance between the “effector” and the regulatory IL-12 isoforms is found ex vivo in cells from septic patients. This imbalance in IL-12 isoform expression may be part of a response to control excessive inflammation, but it also may make patients susceptible to secondary infections.

DENDRITIC CELL ABNORMALITIES IN EXPERIMENTAL TRYPANOSOMIASIS: Chagas disease occurs in many parts of South and Central America, and it is a leading cause of heart disease in endemic areas. It is caused by persistent infection with the hemoflagellate parasitic protozoa, *Trypanosoma cruzi*. The mechanisms by which the parasite evades host immunity and becomes established in host tissues are of high interest for understanding the pathophysiology of the disease manifestations. In this issue, **Chaussabel et al** have studied the effect of experimental *T. cruzi* infection on the migration and maturation of dendritic cells, which are considered to be critical for the initiation of host immune responses (Lab Invest 2003, 83: 1373–1382). Although splenic dendritic cells increase in number during the course of acute infection, dendritic cell maturation, co-stimulatory molecule expression, and migration decrease over time. These effects seem to be important functionally because the splenic white pulp was markedly depleted of both CD4+ and CD8+ T cells during the peak of infection. This deficit in dendritic cell function may account in part for the ability of *T. cruzi* to escape immune destruction and establish a state of persistent infection in the host.