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INSIDE LAB INVEST

CHECK OUT CGH BAR CODING FOR TUMOR TYPING: Comparative genomic hybridization (CGH) is probably the best way to obtain comprehensive overview of the structural alterations present in human tumors. Combined with careful selection of the cells to be analyzed, it provides a reliable method for uncovering recurrent structural alterations that characterize a specific tumor histotype and facilitates the construction of a genotypic nosology. It is quite likely that broad morphological categories, such as malignant fibrous histiocytoma, will be found to be composed of tumors with different genotypic profiles, CGH profiles that can be related perhaps to other, better-differentiated histotypes. The power of CGH is well proven, and it is an efficient, albeit delicate, first step toward discovering candidate loci implicated in the pathogenesis of cancer. Not surprisingly, highly specialized groups have extended and augmented the resolutive power of CGH by using multiplex-fluorescence in situ hybridization (M-FISH) on metaphase spreads and by the careful selection of yeast artificial chromosome (YAC) probes recognizing closely spaced or overlapping regions of chromosomal bands. In this issue (*Lab Invest* 2000;80:1031–1041) **Speicher et al** show how chromosomal bar coding, in this case specifically for chromosome 12, can reveal preferential break sites within specific bands, a finding out of the reach of conventional CGH. We can expect that, with the widespread use of high resolution tumor genotyping approaches, we will gain valuable information about the pathogenesis of tumors.

BLOOD TESTS FOR CANCER? A major challenge in diagnosis and treatment of cancer is the limited sensitivity of techniques for the initial detection and monitoring of tumors. The ideal would be a sensitive and specific blood test for cancer. Although it seems unlikely that this will be achieved, reverse transcriptase-polymerase chain reaction (RT-PCR) assays do provide a general and sensitive method for detection of ectopic tumor cells in blood or bone marrow. There are a number of epithelial markers that would appear to be good prospects for detection of carcinoma cells, but in practice their utility may be limited by the extent to which they are expressed at low levels in blood cells. Recently, Zach, Lutz, and co-workers (*J Clin Oncol* 1999;17:2015) determined that human mammaglobin (hMAM) RNA can be found in blood from patients with breast cancer. In this issue (*Lab Invest* 2000;80:1071–1079) **Grunewald et al** compare the utility of RT-PCR screening for RNA from hMAM with two epithelial markers expressed in breast cytokeratin-19 and epidermal growth factor receptor. Although CK-19 mRNA was present in a large fraction of blood samples from patients with invasive breast cancer, it was also present in many blood samples from healthy volunteers. In contrast, hMAM RNA was detected in 8% of patients with invasive breast cancer but not in control samples. Moreover, hMAM expression was generally associated with involvement of multiple axillary lymph nodes or with distant metastases. Because the most difficult treatment decisions involve node-negative cases, it will be of considerable interest to determine whether the detection of hMAM mRNA in blood from two node-negative patients identifies a high-risk subgroup. Whether hMAM measurements will be useful for monitoring the response to therapies or anticipating frank relapse also remains to be determined. The rapid pace of RNA expression profiling of tumors and normal cells using DNA chips and cDNA arrays will identify a battery of tissue- and tumor-specific markers that may be useful in marking blood-borne tumor cells. It is only a matter of time before the limits of this technique are realized. At minimum, these assays may facilitate the detection of metastasis and the monitoring of treatment efficacy. If the efficiency of the colonization of blood-borne metastases at distant sites is low enough, there is a possibility that the monitoring of blood for tumor cells will locate tumors even in early stages of progression.

STATINS: MULTIFUNCTIONAL DRUGS FOR A RANGE OF DISEASES? In addition to their cholesterol-lowering effects, the beneficial effects of statins on the reduction of adverse cardiovascular events has been attributed, in part, to their anti-inflammatory properties. Several studies have suggested that treatment with statins affects nonlipid determinants of the atherosclerotic process. Previous studies have indicated that modulation of mevalonate and isoprenoid synthesis affects the apoptotic rate of rat vascular smooth muscle cells and monocytic cell cytokine production, both of which are believed to be of importance in the development of atherosclerotic plaque. These data raise the possibility of the use of statins in the treatment of the proliferative and inflammatory aspects of cardiovascular disease in nonhyperlipidemic patients, in addition to its use in hypercholesterolemic patients. In this issue, **Romano et al** (*Lab Invest* 2000;80:1095–1100) demonstrate the inhibition of monocyte chemotactic protein-1 (MCP-1) synthesis by statins. Using both in vivo and in vitro models, the authors demonstrate that lovastatin and simvastatin both cause a dose-dependent inhibition of MCP-1 production in peripheral blood mononuclear cells and in human endothelial cells. This statin-mediated inhibition could be overcome by the addition of mevalonate, suggesting that mevalonate-derived products are involved in chemokine production. Additionally, using a murine air-pouch model, they demonstrate that oral administration of lovastatin or pravastatin, at levels that inhibited hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase but did not affect blood cholesterol, reduced lipopolysaccharide (LPS)-induced leukocyte recruitment and exudate MCP-1 production. The ability of statins to modulate cytokine production (inhibit MCP-1 production), and thus inflammatory cell infiltration, represents a potentially important additional mechanism of action in this class of drug. These findings and additional discoveries regarding these mechanisms of action raise the possibility that statins may have other, yet to be discovered, therapeutic uses.

LOOKING BACK ON HCV: It is now just over a decade since hepatitis C virus (HCV) was first identified as a cause of non-A, non-B hepatitis. Hepatitis C virus infection is the most common blood-borne chronic infection in the United States and has been estimated to affect almost 2% of the population. Although the etiological role of HCV in hepatitis is firmly established, it has also been proposed that HCV infection is linked to several nonhepatic syndromes. It has recently been discovered that HCV can infect the myocardium, which has led to active investigation of the possible role of HCV in myocarditis and cardiomyopathy. Using reverse-transcription followed by polymerase chain reaction (RT-PCR), **Matsumori, Sasayama, and colleagues** have evaluated the prevalence of HCV RNA in an archival series of fixed embedded sections of hearts from patients with cardiac disease (*Lab Invest* 2000;80:1137–1142). Remarkably, they were able to detect HCV in samples dating back up to 20 years, and it was possible to determine nucleotide sequences for several of these. The results support, but do not prove, a link of HCV to cardiomyopathy. This work verifies the feasibility of retrospective analysis of HCV infection. Retrospective analysis of HCV prevalence, tissue distribution, geographical distribution, and nucleotide sequences will facilitate investigation of the role of HCV in cardiac disease, the association of HCV with other diseases, and the epidemiology and evolution of this important, but poorly understood, virus.