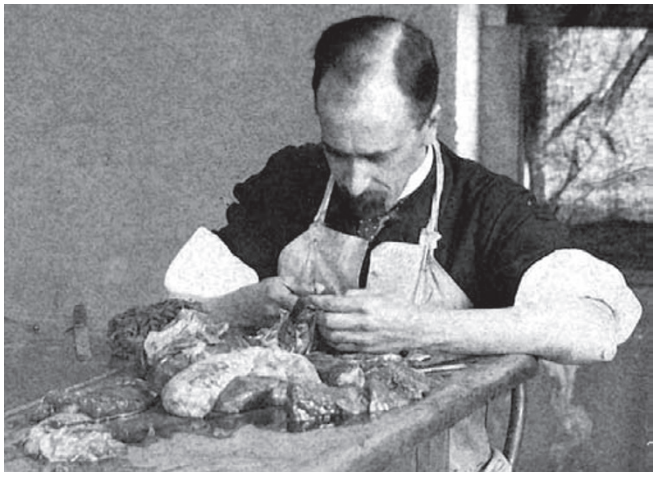
Laboratory Investigation (2008) 88, 2-3

INSIDE LAB INVEST

doi:10.1038/labinvest.3700711



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The pathology of mice and men

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The annals of medical research over the past two centuries make abundantly clear the importance of animal models of human disease. Since the mid-1800s, biomedical investigators have moved smoothly between animal models in the experimental laboratory, and the clinical arena in which these diseases are manifest. The past quarter century has seen the extraordinary demolition of speciation as a barrier to molecular research. Indeed, it is the very similarity of the genetic makeup of not only mammals, but also lower vertebrates, invertebrates, and single-celled organisms, that now provides vast information relevant to the human condition. In this issue, Cardiff and colleagues examine an unfortunate by-product of our recent molecular successes: the apparent elimination of comparative pathology. At the same time that molecular science has bridged the species as never before, a key element of the research workforce has atrophied: the systems scientist who is the pathologist. One of the fundamental truths of disease—animal or human—is that it exhibits morphological features at some point in its course. Examination of morphology is an important benchmark against which animal models of disease must be measured. Study of these animals is the domain of the molecular morphologist: the pathologist. This is particularly true in the realm of murine pathology, in which the populations of mouse colonies under study may exceed the number of faculty, staff, and students at a university.

In essence, expert pathologists are requisite members of any research team that is establishing a murine model of human disease, and they may be of critical value at many points along the way as the animals are studied. Cardiff and colleagues examine the dynamics that have led to a dearth of murine experimental pathologists, whether veterinary or human pathologists. They call for the establishment of a visible scientific community of trained murine pathologists, a proposal that the editors of this journal wholeheartedly endorse.

Stem cell homing and the activated endothelium

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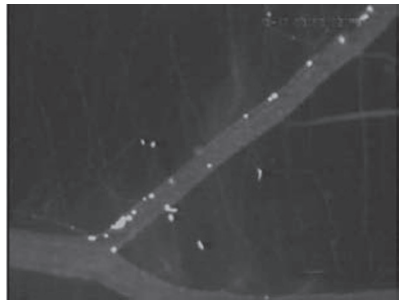
One of the fundamental questions in stem cell biology is how stem cells in distant organs (e.g., bone marrow) could be recruited and migrated to injured tissues, putatively supporting regeneration of the tissues. Chemokines have been at the center of attention for the mechanism; more specifically, stromal-cell-derived factor-1 alpha (SDF-1α) has been implicated in numerous publications. For instance, the upregulation of SDF-1α in infarcted myocardium is closely related to the recruitment of circulating stem cells expressing CXCR4, the receptor of SDF-1α, and thence, to improvement of cardiac function. However, it would be too simplistic to speculate that SDF-1α alone recruits stem cells, considering the fact that the SDF-1α–CXCR4 interaction is involved in cell migration events quite ubiquitously.

In this issue, Kaminski *et al* demonstrate that inflammatory endothelial activation by tumor necrosis factor-alpha is required for c-kit$^+$ progenitor cells to firmly adhere to endothelial cells, over and above having SDF1-α as a chemoattractant. Furthermore, activation of endothelial nitric oxide synthase is likely involved in stem cell adhesion to endothelial cells. Although further studies are necessary for full understanding of molecular mechanisms, the present study provides an additional important clue as to how circulating stem cells successfully home to the injured tissues.



Disclosing the identity of hepatocyte paraffin 1 antigen

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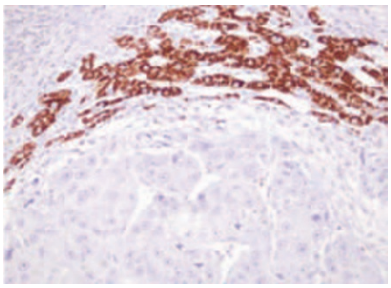
Hepatocyte paraffin 1 (Hep Par 1) is one of only a few antibodies that are relatively cell-lineage-specific. Since its generation in 1993 by Wennerberg and colleagues using antigen derived from a formalin-fixed failed allograft liver, Hep Par 1 has become a widely used diagnostic marker in surgical pathology to determine the hepatocellular origin of neoplasms. Surprisingly, the antigen recognized by this monoclonal antibody remained elusive for more than a decade. In this issue, Butler *et al* solve the puzzle by

showing that Hep Part 1 antigen is a rate-limiting enzyme of the urea cycle, carbamoyl phosphate synthetase 1 (CPS1). Using immunoprecipitation, mass spectrometry, and database search, the authors demonstrated that the peptide sequences of the protein immunoprecipitated by Hep Par 1 matched that of CPS1 with a very high degree of probability. The link was further established by combined immunoprecipitation–western blot analysis with a reciprocal recognition of the protein by both Hep Par 1 and a polyclonal anti-CPS1 antibody, and by immunohistochemistry performed on a hepatocellular carcinoma, a gastric adenocarcinoma with hepatoid differentiation, and several yolk sac tumors with similar staining patterns for both antibodies.



The findings of this study not only may satisfy the curiosity of pathologists, but also raise intriguing questions regarding the physiologic and pathogenetic roles of CPS1. The observation of CPS1 expression in small-bowel enterocytes suggests that CPS1 is more than just a urea cycle enzyme, although the possibility cannot be entirely excluded that the antibodies may cross-react with another epitope specific to the small intestine. CPS1 may also serve a role in carcinogenesis because its expression is transcriptionally downregulated in hepatocellular carcinoma cell lines and aberrantly upregulated in a small subset of non-hepatocellular neoplasms (as demonstrated by Hep Par 1 immunostains in other studies). This study has thus provided the rationale for future investigations to elucidate additional potential functions of CPS1.

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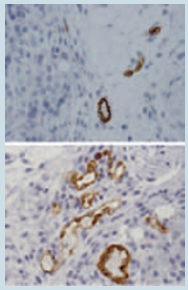
nature.com/pathology

MicroRNA-10b: The Twist that leads to metastasis MicroRNAs are a new class of regulatory RNAs that impact diverse cellular functions. A recent article in *Nature* suggests that one microRNA, miR-10b, may contribute to tumor metastasis. MiR-10b is highly expressed in breast cancer cell lines that form tumors with metastases in mice but not in cell lines that form tumors without metastases. Transgenic expression of miR-10b in a non-metastasizing line conferred metastatic behavior *in vivo*. The study continues to show that miR-10b, whose expression is induced by the transcription factor Twist, inhibits translation of homeobox D10 and increases expression of known pro-metastatic genes. Moreover, miR-10b expression correlates with progression in breast cancer patients. This work sheds new light on the role of microRNA in cancer progression and may, in the future, provide a new clinical assay to identify tumors at increased risk of aggressive behavior.

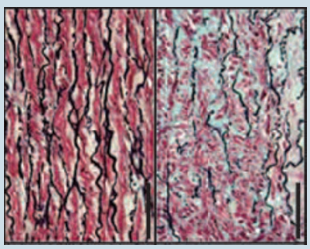


Nature 2007;449:682–688; doi:10.1038/nature06174

A serum assay for Alzheimer's disease? The diagnosis of Alzheimer's disease remains not only one of the most alarming diagnoses for patients but also one of the most difficult for physicians to determine. As a result, many patients with mild cognitive impairment suffer the fear of not knowing whether they will progress to Alzheimer's disease. A recent report in *Nature Medicine* studied 259 archived plasma samples from control subjects and individuals with presymptomatic to late-stage Alzheimer's disease. The abundance of 120 known signaling proteins was measured and data analyzed using an unsupervised clustering algorithm. Eighteen serum proteins whose expression levels predicted progression to Alzheimer's disease within 2 to 6 years were identified. This observation could help improve the management of individual patients as well as the identification of patients to be included in studies of therapies to slow disease progression.

Nature Medicine 2007;13:1359–1362; doi:10.1038/nm1653

Smooth muscle α-actin: not just for immunohistochemistry anymore! Smooth muscle α-actin is a protein that is well known to most surgical pathologists. A recent report in *Nature Genetics* shows that smooth muscle α-actin is also essential to vascular structure. Linkage analysis of a family with autosomal dominant inheritance of thoracic aortic aneurysms and dissections identified a mutation in smooth muscle α-actin. This observation was validated in several other families, with the conclusion that missense mutations in smooth muscle α-actin cause 14% of inherited thoracic aortic aneurysms and dissections. Mutations in the β-myosin heavy-chain gene *MYH11* have also been linked to this disease, suggesting that contraction of vascular smooth muscle cells, which regulates blood pressure and flow, requires cyclic interactions between α-actin and β-myosin heavy chain and is critical to maintenance of aortic integrity.



Nature Genetics, published online 11 November 2007; doi:10.1038/ng.2007.6

TTF1 is a commonly mutated tumor suppressor in lung cancer We are now aware of many mutations and translocations that are specifically associated with specific soft tissue and hematopoietic malignancies, but what about adenocarcinomas? In general, adenocarcinomas have a broad array of genetic and cytogenetic abnormalities accumulated over time, making it difficult to determine which occurred first or the relative contributions of each mutation. As a step toward better understanding of carcinogenesis in the lung, a large group has now performed gene chip studies on more than 500 snap-frozen lung adenocarcinoma resection specimens. These 26 gains or losses involve large areas of autosomal chromosomes, including amplification of TTF1 (also known as NK2 homeobox 1 and TITF1) on 14q13.3 in 12% of tumors. *In vitro* studies showed that knockdown of TTF1 expression reduced anchorage-independent growth and viability of some lung adenocarcinoma cell lines.

Nature, published online 4 November 2007; doi:10.1038/nature06358