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Alien vs Predator: When nosology and genetics collide, different is not always different

Pathologists have long struggled with the limitations of morphology in the diagnosis of neoplasia. For the nonexpert, this struggle is particularly intense in the field of soft-tissue pathology. Here, an astounding array of mesenchymal morphologies is accompanied by an equally perplexing lexicon of nosologic entities. The many descriptors such as ‘fibromyxoid’, ‘fibrohistiocytic’, ‘myxohyaline’, and so forth represent our best attempt to characterize a morphologic appearance, infer a cell lineage, and ultimately suggest a biological activity. The great promise of molecular genetics for pathology is that it may provide more objective data on which to base biologically and clinically relevant classification systems of neoplasia, and hence provide new insights into molecular pathways relating to pathogenesis. Inside this issue, **Idbaih et al**¹ (p. 176) use comparative genomic hybridization to evaluate chromosome imbalances of two high-grade sarcomas: the pleomorphic liposarcoma and the myxoid malignant fibrous histiocytoma (myxoid MFH; also called ‘myxofibrosarcoma’). Although these two tumor types are rather well-defined nosologic entities in diagnostic pathology, some morphologic overlap may occur such as the presence of lipoblast-like cells (‘pseudolipoblasts’) in the myxoid MFH. When clustering software was used to identify significant differences in the genetic characteristics of these tumors, none could be demonstrated, suggesting a genetic relationship between these two entities. However, the chromosome imbalances were significantly different from other poorly differentiated soft-tissue sarcomas such as leiomyosarcoma, suggesting a distinct pathway of tumorigenesis for both pleomorphic liposarcoma and myxoid MFH. The data provided by this study will help guide further efforts to identify genes affected by the reported genomic aberrations. Although the ‘alien’ and ‘predator’ are genetically similar, tools for their ultimate defeat may be at hand.

Reference

- 1 Idbaih A, Coindre J-M, Derré J, et al. Myxoid malignant fibrous histiocytoma and pleomorphic liposarcoma share very similar genomic imbalances. *Lab Invest* 2005;85:176–181.

Early or late? LOH can be a Catch 22

This issue of *Lab Invest* features two studies that suggest an association between loss of heterozygosity (LOH) on chromosome 22q and tumor development, progression, or metastasis in cancers. The first paper shows that LOH on chromosome 22q plays a role in early stages of tumor formation as well as late tumor progression in gastrointestinal stromal tumors (GISTs), while a second study demonstrates that 22q LOH also occurs in the progression to secondary glioblastomas. While the specific genes involved are likely different, these studies add to the growing list of tumors associated with LOH on 22q, including breast, ovarian, pancreatic, and colorectal cancer.

GISTs are mesenchymal tumors of the gastrointestinal tract which share histologic features with smooth muscle tumors and, in a subset, autonomic nerve tumors. Neoplastic growth in GISTs is generally driven by pathologic activation of c-KIT or platelet-derived growth factor receptor alpha. However, other genetic changes, such as loss of genetic material from chromosome 22, have also been documented in GISTs. In this issue of *Lab Invest*, **Lasota et al**¹ (p. 237) evaluate a group of well-characterized GISTs for LOH on chromosome 22q in order to identify common regions of deletions, which may harbor genes important for GISTs pathogenesis. LOH was evaluated using PCR-based microsatellite markers and capillary gel electrophoresis. The authors found that 30% of cases showed sufficient LOH to implicate total loss of chromosome 22q. Another 50% of cases revealed LOH of markers clustered in different loci, suggesting simultaneous involvement of up to three multiple different regions of 22q. Similar LOH patterns were seen in both early- and late-stage tumors, suggesting that LOH occurs early in tumor development. However, since the frequency of LOH was significantly greater in malignant vs benign GISTs, it is possible that some LOH sites are correlated with, or even cause, malignant progression in GISTs. Based on this study, at least three different regions harboring genes important for GISTs development can be defined and should be a subject of further molecular genetic studies.

A second study by **Nakamura et al**² (p. 165) analyzed primary and secondary glioblastomas for LOH on 22q, which had been previously demonstrated in a nonselected series of glioblastomas. Glioblastoma is the most frequent and most malignant tumor arising in the human central nervous system. While the majority of these tumors are primary glioblastomas, or those which develop after a short clinical history without clinical or histo-

pathological evidence of a less malignant precursor lesion, a subset represents secondary glioblastomas. The latter develops from low-grade diffuse or anaplastic astrocytomas. Genetic analyses suggest that primary and secondary glioblastomas develop through different genetic pathways. Thus, the objective of this particular study was to compare LOH on 22q in primary and secondary glioblastomas. The authors performed a high-density LOH analysis using 31 polymorphic microsatellite markers that spanned 22q. They screened a series of diffuse astrocytomas, anaplastic astrocytomas, primary glioblastomas, and secondary glioblastomas proven to have evolved from lower grade astrocytomas. LOH was found at one or more loci in 33% of low-grade (grade II) diffuse astrocytomas, 40% of anaplastic astrocytomas, 41% of primary glioblastomas, and 82% of secondary glioblastomas. This demonstrates more frequent LOH at 22q in glioblastomas arising from lower grade precursor lesions, that is, secondary glioblastomas; as opposed to *de novo* lesions, that is, primary glioblastomas and astrocytomas. Like GISTs with LOH at 22q, the specific genes involved remain to be identified in glioblastomas and astrocytomas. However, it is interesting to note that 22 of 23 secondary glioblastomas shared a deletion in the same small region of 22q12.3 that is home to a known tumor suppressor gene, tissue inhibitor of metalloproteinases-3 (*TIMP-3*). Thus, this study provides the first evidence that this site is frequently involved in the progression from low-grade astrocytomas to secondary glioblastomas. The data also suggest that *TIMP-3* is a specific target whose mutation predisposes to progression of astrocytomas to secondary glioblastomas.

While it is premature to consider making diagnostic and therapeutic decisions on the basis of LOH at these sites in GISTs and secondary glioblastomas, the data presented in these studies hold the promise that LOH analysis will one day become as routine as immunohistochemistry. Whether our labs are ready for that evolution triggered by our own studies may be the real 'Catch-22'.

References

- 1 Lasota J, Wozniak A, Kopczynski J, *et al*. Loss of heterozygosity on chromosome 22q in gastrointestinal stromal tumors (GISTs). A study on 50 cases. *Lab Invest* 2005;85:237–247.
- 2 Nakamura M, Ishida E, Shimada K, *et al*. Frequent LOH on 22q12.3 and *TIMP-3* inactivation occur in the progression to secondary glioblastomas. *Lab Invest* 2005;85:165–175.

HIV and a broken heart

HIV viral protein R (Vpr) encodes a unique 96 amino-acid polypeptide that is necessary for infection of macrophages. In mononuclear cells, Vpr causes G2/M cell cycle arrest and apoptosis. Conversely, mutant Vpr is associated with nonprogressive HIV infection and impaired apoptosis. Since Vpr also circulates freely in plasma, paracrine effects from this protein could impact numerous cellular functions in the host. While Vpr has been implicated in the development of congestive heart failure (CHF) and dysrhythmias in AIDS, a mechanism to explain these clinical observations has been lacking. In this issue of *Lab Invest*, **Lewis *et al***¹ (p. 182) employ a cardiac-targeted Vpr to dissect the effects of this HIV gene product on the structure and function of the heart, without the systemic effects of AIDS. The cardiac targeting was achieved via the α -myosin heavy chain promoter. The hearts of transgenic cardiac-targeted Vpr mice (TG) and of wild-type littermates were evaluated histopathologically, ultrastructurally, and molecularly via RNA microarray analysis and quantitative RT-PCR. In living animals, cardiac function was evaluated by cardiac magnetic resonance imaging and electrocardiograms. The authors found that targeted cardiac Vpr caused profound heart failure and dysrhythmias. The TG animals developed atrial cardiomyocyte proliferation with aberrant mitoses and defects in cardiomyocyte nuclear structure, atrial mesenchymal tumors, and the phenotype worsened temporally and with gene dosage. Thus, the presence of HIV viral protein R appears to have a direct biological effect on the heart. Future studies with this Vpr TG may elucidate pathophysiological mechanisms that relate the effects of Vpr-induced alterations in cardiac and noncardiac cells. This work may also offer some insights into mechanisms of cardiomyopathy in AIDS, a problem that may be increasingly important with increased survival of patients with HIV infection owing to improved therapeutic regimens.

Reference

- 1 Lewis W, Miller YK, Haase CP, *et al*. HIV viral protein R causes atrial cardiomyocyte mitosis, mesenchymal tumor, dysrhythmia, and heart failure. *Lab Invest* 2005;85:182–192.