Pathology Elsewhere

Laboratory Investigation (2005) **85**, 163–164. doi:10.1038/labinvest.3700226

Hypomethylation of *maspin* in pancreatobiliary tract carcinomas: a tissue-specific epigenetic event

Maspin, a serine protease related to the SERPIN family, was originally identified in normal human mammary duct epithelium but it was silenced or its expression was greatly reduced in breast cancer. Previous studies have shown that *maspin* could inhibit cell motility, tumor invasion, and metastasis of breast and prostatic carcinomas, and loss of *maspin* has been associated with a poor prognosis. Thus, it was once considered a tumor suppressor gene. However, in contrast to breast cancers, *maspin* was expressed in pancreatic, lung, prostatic, and ovarian carcinomas, although not in their adjacent normal epithelium. This paradoxical expression pattern of *maspin* is not a rebuttal to the above concept; but rather suggests a tissue-specific mechanism of controlling *maspin* expression.

Tissue-specific gene expression can be established and maintained by DNA methylation, an epigenetic event. Holiday and Riggs first proposed this concept more than 25 years ago, now well supported by further studies. In this specific instance, the *maspin* promoter contains CpG islands that can be hyper- or hypomethylated. Hypo- or hypermethylation of a promoter turns gene transcription on or off, depending upon tissue types. In pancreatic carcinoma, hypomethylation of the *maspin* promoter leads to *maspin* expression, normally suppressed in the pancreatic duct epithelium. It has been recognized that an epigenetic modification such as DNA hyper- or hypomethylation is as important as genetic alterations including mutations, deletions, and amplification in tumor development and progression. Inhibition of methylation of the *maspin* promoter is a frequent event in pancreatic carcinoma, suggesting that the *maspin* gene may play an important role in its development.

The reason why cancers of different origins have different methylation status of the *maspin* promoter remains unclear. It is hypothesized that *maspin* may have a rather different function in different tissues, or that this epigenetic event may be a bystander effect of global loss of tissue-specific methylation homeostasis. The latter hypothesis has been contested by several studies. **Sato et al.**¹ using DNA microarray technique analyzed the global gene methylation profile in primary pancreatic carcinomas and several related cell lines. They demonstrated that *maspin* was among the 218-hypomethylated candidate genes among the 1485

identified transcripts, although it was absent from the laser-captured microdissected normal pancreatic duct epithelium. Artificial induction of methylation by 'epigenetic-modifying agents' (DNA methyltransferase inhibitor and histone deacetylation inhibitor) could 'turn on' the demethylation mechanism and resulted in *maspin* expression. Two other genes, trefoil factor and lipocalin 2, were also frequently hypomethylated in pancreatic carcinoma cell lines, but not in breast cancer cell lines. These data suggested that a tissue-specific methylation mechanism might contribute to this paradoxical *maspin* expression pattern in different tissues and that hypomethylation of *maspin* might be an event in the cascade of loss of methylation homeostasis or a consequence of genome-wide genetic instability in pancreatic carcinoma.

In this issue of *Lab Invest*, **Fujisawa et al.**² demonstrated by immunohistochemical analysis that biliary duct carcinomas (cholangiocarcinomas, gallbladder carcinomas), which histogenetically, morphologically, and genetically were the pancreatic counterparts, also expressed *maspin* by a similar mechanism. In contrast, hepatocellular carcinoma (HCC) and HCC cell lines, which also originated from the liver, did not express *maspin*. As a matter of fact, induction of *maspin* expression in some HCC cell lines required factors other than the usual 'epigenetic-modifying agents,' as mentioned above. These data confirm the concept that the expression of *maspin* protein is controlled by a tissue-specific methylation mechanism, and that it may have different functions in different tissues. This concept provides a molecular basis to search for a tissue-specific cancer therapy by targeting methylation of a gene critical for tumor development and progression.

Ruliang Xu, MD, PhD

References

- 1 Sato N, Fukushima N, Matsubayashi H, et al. Identification of *maspin* and *S100P* as novel hypomethylation targets in pancreatic cancer using global gene expression profiling. *Oncogene* 2004;23:1531–1538.
- 2 Fujisawa K, Maesawa C, Sato R, et al. Epigenetic status and aberrant expression of the *maspin* gene in human hepato-biliary tract carcinomas. *Lab Invest* 2005;85:214–224.

Can polio-like virus emerge from human enterovirus C?

Based on the current viral classification scheme, there are five Enterovirus species: Poliovirus (PV) and Human enterovirus A, B, C, and D (HEV-A to -D).

The three known PV serotypes constitute the species Poliovirus, whereas Coxsackie A virus serotypes 1, 11, 13, 15, 17, 18–22, and 24 make up Human enterovirus C (HEV-C). Despite distinct pathogenic profiles (PV causes poliomyelitis and HEV-C causes upper respiratory infections), these viruses show homogeneity at sequence level with evidence of genetic intermingling between PV and HEV-C to the extent that it is impossible to distinguish whether sequences of PV nonstructural proteins originated from HEV-C or *vice versa*. The capsid sequences comprise the only genome region to clearly delineate PV and HEV-C, which correspond to the groups' differential receptor preferences: PVs use CD155, whereas many HEV-Cs recognize human intercellular adhesion molecule 1 (HsICAM-1).

Dufresne *et al*¹ conducted a study using Coxsackie virus A21 (CAV21), a prototypical HEV-C serotype that uses HsICAM-1 as a cellular receptor, in mouse models with ectopic expression of this receptor. Intramuscular inoculation of CAV21 in these mice produced a classic paralytic poliomyelitis. Although the pathognomonic features of CAV21 and PV-induced poliomyelitis in HsICAM-1 and CD155 transgenic mice, respectively, are identical, the symptoms and progression are far more benign in the former. CAV21-infected HsICAM-1 transgenic

mice developed regionally restricted spinal cord lesions and mild motor dysfunction that never progressed beyond the initially affected limb. These differences may relate to the viral receptors or may reflect PV's superior ability to persevere and spread in the central nervous system, which is facilitated by retrograde axonal transport.

The investigators hypothesized that capsid may be responsible for the deficient neuroinvasion by CAV21, because it exhibits the most genetic divergence between HEV-C and PV. It is then possible that if CAV21 acquire a 'PV-like' capsid, an enhanced capacity for neuroinvasion could result. This study suggests that HEV-C, with its adaptable genome, could represent a genetic pool from which novel PV-like variants could emerge to fill the evolutionary void generated by planned worldwide eradication of PV.

Arief Suriawinata, MD

Reference

- 1 Dufresne AT, Gromeier M. A nonpolio enterovirus with respiratory tropism causes poliomyelitis in intercellular adhesion molecule 1 transgenic mice. *Proc Natl Acad Sci USA* 2004;101:13636–13641.