Review

UHN Microarray Centre

Looking into eye cancer: The identification of genes that modify metastatic risk

Review of: Onken MD, Worley LA, Harbour JW. A Metastasis Modifier Locus on Human Chromosome 8p in Uveal Melanoma Identified by Integrative Genomic Analysis. Clin Cancer Res 2008, 14(12):3737

As metastasis is the leading cause of death in cancer patients, identifying therapeutic targets that interfere with the metastatic process is critical (1). Many oncogenes and tumour suppressor genes have been identified, but only about 10 metastasis suppressor genes have been identified (2). Uveal melanoma is a common intraocular malignancy that results in aggressive metastases in about half of all cases (3). This particular cancer is valuable for studying metastasis as it has a well characterised gene expression signature associated with metastasis and the metastasis occurs mostly by the hematogenous route rather than by local invasion or lymphatic dissemination (1,3). The two distinct expression signatures of uveal melanoma have already been described (4). Tumours with the class 1 signature have a very low risk of metastasis, whereas those with the class 2 signature have a high risk of metastasis. In this study, the class 2 tumours were further segregated into two subgroups, class 2A and class 2B (1). Class 2B tumours were associated with more rapid onset of metastasis than class 2A tumours.

Onken and colleagues have previously reported that the development of the class 2 gene expression signature is usually accompanied by the deletion of chromosome 3, suggesting that one or more genes on chromosome 3 may be associated with metastatic progression (5). The purpose of this current study was to identify genes that modify metastatic risk in uveal melanoma. To this end, researchers analysed 53 primary uveal melanomas by various integrative genomic methods.

Array CGH and SNP-based detection of loss of heterozygosity

Using array CGH, chromosomal copy number changes were assessed in 19 of the class 2 tumours. Of the various copy number changes identified, the only alteration that correlated with time to metastasis was 8p loss. SNPs across chromosome 8p were interrogated for loss of heterozygosity to further define the minimal deleted region, which consisted of a 10Mb stretch from 8p22 to 8p12. Leucine zipper tumour suppressor-1 (*LZTS1*), one of the 11 genes located within the deleted region, was most strongly linked to rapid metastasis.

Global DNA methylation profiling

In addition to the deletion of chromosome 8p12-22, DNA hypermethylation of the corresponding region of the retained hemizygous 8p allele was associated with more rapid metastasis. DNA from six tumours was interrogated using methyl-DNA binding columns followed by hybridisation of the enriched samples to UHNMAC HCGI12K arrays. Global DNA methylation profiling showed that the *LZTS1* promoter was hypermethylated and silenced in rapidly metastasising tumour cells and not in slowly metastasising or non-metastasising cells.

Gene expression profiling

The expression of *LZTS1* was further evaluated. Uveal melanoma cells overexpressing *LZTS1* exhibited decreased invasion and motility while cells depleted of *LZTS1* using small interfering RNA exhibited increased motility. The proliferation rate in uveal melanoma cells was not altered by modulation of *LZTS1* mRNA levels. Other studies have reported that LZTS1 functions, in part, as a mitotic regulator (6) and can inhibit cancer cell growth through regulation of mitosis (7).

Using various integrative genomic methods, Onken and colleagues have shown how genetic modifiers of metastatic risk can be identified in human cancers. This study reveals that the silencing of a region on chromosome 8p modifies the metastatic efficiency of class 2 primary uveal melanomas.

References

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