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Using Transcriptomics to Define Metastatic Risk in Uveal Melanoma

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Uveal melanoma (UM) is the most common primary intraocular tumour in adults. About half of all UM patients develop metastases, usually to the liver, which are often fatal <2 years following diagnosis. Chromosomal aberrations, in particular loss of one copy of chromosome 3, can stratify patients into low (LR) or high (HR) metastatic risk groups. In this study, we used transcriptomics to define gene and miRNA signatures unique to LR and HR UM patients and to identify signalling pathways, which can be exploited in the development of treatment strategies for metastatic disease.

Total RNA was extracted from 20 UM patients; 10 LR and 10 HR, which was then hybridised to human Affymetrix GeneChip microarrays. Bioinformatic pipelines were used to identify differentially expressed genes and miRNAs, and Ingenuity Pathway Analysis (IPA) was used to determine causal networks. Additional sample mutation analysis was determined using PCR and Sanger sequencing.

Transcriptomic analysis identified 895 differentially expressed genes (fold change >2, $P<0.05$), with 372 genes upregulated and 523 downregulated in the HR c.f LR group. Additionally, 149 miRNAs were differentially expressed with fold change >2; 56 miRNAs were upregulated and 93 downregulated in the HR c.f LR group. The most differentially upregulated genes and miRNAs associated with HR included: HTR2B, ADAM23, RAB31, hsa-miR-371b-5p, hsa-miR-572; whilst those downregulated and associated with LR included: PDE3A, SPP1, CHL1, hsa-miR-509-3p, hsa-miR-506-3p. Validation of a subset of genes and miRNAs by PCR demonstrated concordance with microarray data. IPA identified cancer as the main biological function and highly-upregulated canonical pathways in HR UM, included mTOR and EIF4 signalling; whilst EIF2 signalling was downregulated.

Transcriptomic analysis has identified genes, miRNAs and functional pathways dysregulated in UM which are unique to LR or HR tumours; providing numerous targets for future drug exploration.