An Investigation of miRNAs in the Pathogenesis of Paediatric/Wild-Type Gastrointestinal Stromal Tumour

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Introduction
Geometrical Stomatal Tumours (GSTs) may arise at any age but most commonly occur in men aged 55-65 years old and are characterized by activation of mutations of proto-oncogenic receptor KIT or PDGFRα. These mutations are mutually exclusive and are the initiating events in GST development. Amplification of oncogenes affects a small percentage bear a B-Raf mutation. The remainder are known as wild-type (WT) GSTs. Pedigree are a subset of adults who are typically the first to be diagnosed and have been shown to have increased levels of KiT expression and have similar metastatic behaviour to adult tumours, albeit occurring at a younger age.

While adult GSTs show large scale genomic losses of chromosomes 14q, 11q, 1p and 4p with progression, these changes are not seen in the paediatric setting. Differentially expressed miRNA profiles have also been identified in adult and paediatric GSTs. Strong KIT over-expression is important in a potential therapeutic target, currently being assessed by clinical trials for paediatric GSTs.

WT GSTs can be associated with a number of syndromes: Neurofibromatosis, Carney’s Triad and Carney-Stratakis Syndrome (Carney). Carney’s Triad is the association of GST with syndrome-like syndromes, and is often associated with a high risk of metastatic potential.

Adult Mutant Adult WT Pediatric WT

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Methodology
Sample Cohort
Samples were collected from European and US pathology and oncology colleagues. Age categorization was: <25 years = pediatric, 25-65 years = adult, >65 years = adult mutant cases. The cohort included 30 adult mutant, 15 adult WT and 30 pediatric WT cases.

Validation
Three miRNAs were selected for validation with individual TaqMan® microRNA assays. These were selected based on the above criteria: cut-off difference, target gene and statistical significance. The miRNA chosen for validation were hsa-miR-455-3p, hsa-miR-496 and hsa-miR-542.

Findings
Cluster Analysis shows separation of adult mutant from paediatric/wild-type GSTs. The adult mutant cases are split according to expression of miRNAs on 14q. This split is NOT purely based on genomic 14q status. Adult WT GSTs mainly cluster with paediatric WT cases.

miRNA profiling results for validation

The data were then investigated for potential biological interactions between differentially expressed miRNAs and miRNA expression (based on published expression data) for the comparison: 1) Genes higher in pediatric compared to adult mutant – miRNAs lower in pediatric compared to adult mutant (Pediatric > Adult); 2) Genes lower in pediatric compared to adult mutant – miRNAs lower in adult mutant compared to adult mutant; 3) Genes higher in mutant compared to WT – miRNAs lower in mutant compared to WT; 4) Genes higher in wild-type compared to mutant – miRNAs lower in mutant compared to WT.

Table 1: miRNA expression is significantly greater than expected for adult mutant cases. miRNA expression is significantly lower than expected for adult mutant cases.

Figure 1: A) miRNA profiling results for validation. B) miRNA expression is significantly greater than expected for adult mutant cases. miRNA expression is significantly lower than expected for adult mutant cases.

Table 2: miRNA expression is significantly greater than expected for adult mutant cases. miRNA expression is significantly lower than expected for adult mutant cases.

Table 3: miRNA expression is significantly greater than expected for adult mutant cases. miRNA expression is significantly lower than expected for adult mutant cases.