Exploiting 3-D Models of Salivary Gland Adenoid Cystic Carcinoma to Discover Novel Therapies and Biological Insights

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AdCC is predominantly driven by the activation of the proto-oncogene MYB which encodes a transcription factor that in turns governs cell fate and stem-progenitor cell expansion; key processes subverted in cancer. The development of 3D models of AdCC has provided an unprecedented opportunity to explore a novel link between MYB expression and a neural crest cell fate marker expression.

When AdCC biopsies are examined at the histological level it is evident that the morphology can be mixed with cribriform and solid histotypes. MYB and SOX10 stem cell associated transcription factors appear to be preferentially expressed in the solid histotype tumour cells (Figure 1).

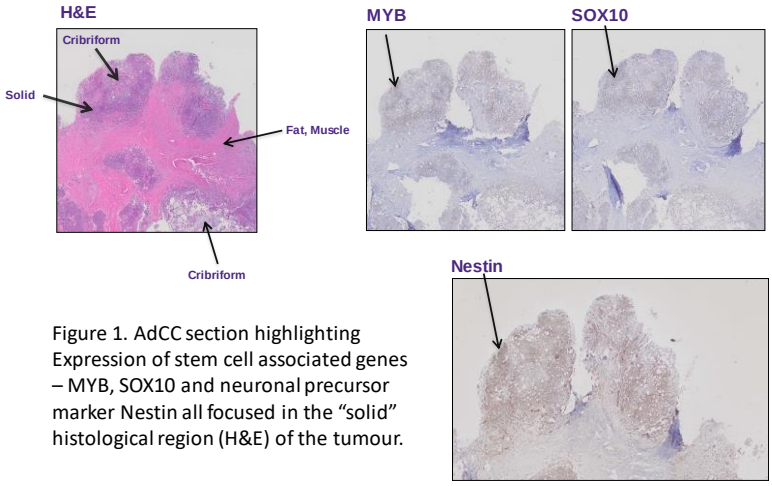

Figure 1. AdCC section highlighting Expression of stem cell associated genes – MYB, SOX10 and neuronal precursor marker Nestin all focused in the "solid" histological region (H&E) of the tumour.

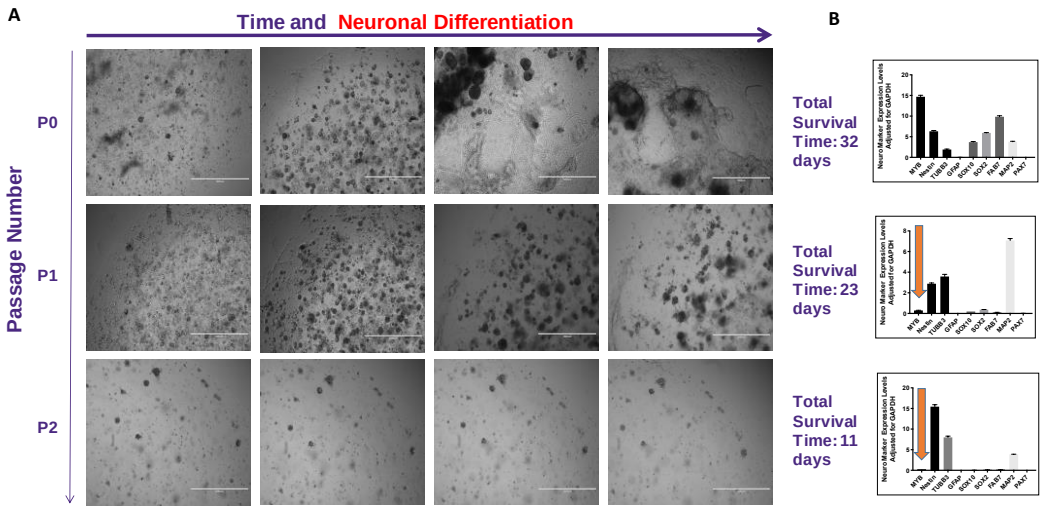

Figure 2. (A) Tumouroids are readily developed from AdCC tumour biopsies however they have a propensity to differentiate along the neural pathway. (B) MYB is typically associated with undifferentiated populations of progenitor cells in multiple tissues and is lost when tumouroids initiate a neuronal transcriptional program.

Consistent with the neural crest cell of origin of this tumour we examined this relationship by profiling of tumouroid cultures for MYB and neuronal and stem cell gene expression signatures (eg, SOX10, CD133, Nestin, NOTCH1, MAP2, GMP6b, FAB7, TUBB3) (Figure 2).

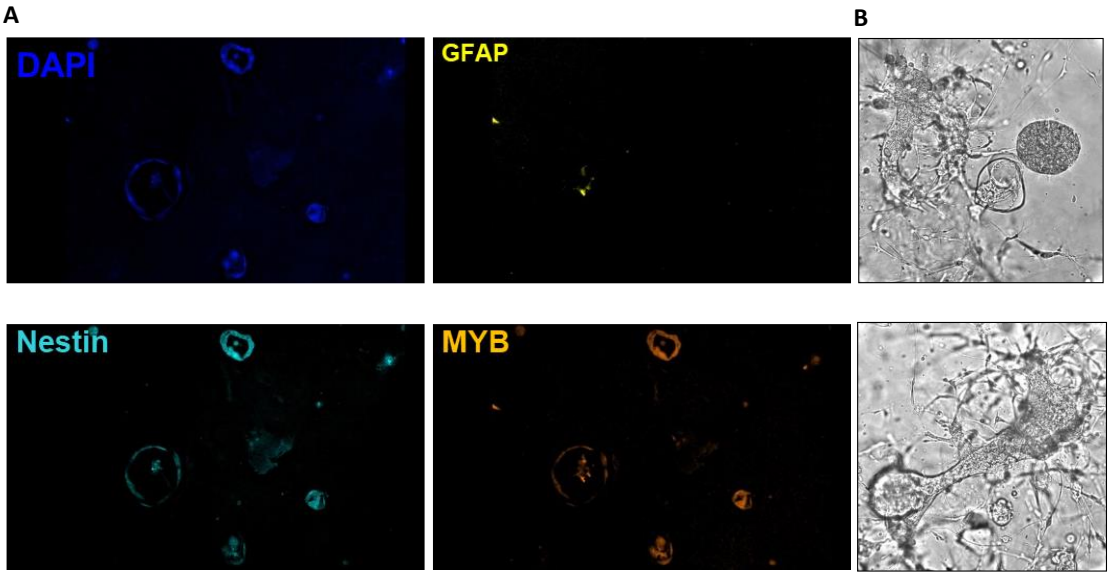

Figure 3. (A) Tumouroids developed from AdCC tumour biopsies allow us to track the differentiation process and temporal gene expression of relevant genes. (B) Over time the tumouroids loose the capacity to be propagated because the terminally differentiate into neuronal like structures.

In parallel we have undertaken a comprehensive multiplex immunohistochemistry analysis of tumouroids of these gene markers (Figure 3). In rarer situations, AdCC is driven by a MYB family member – MYBL1 (A-MYB) and here we explored the reciprocal situation where either but both family members are expressed. This information is highly relevant to understanding outcomes of reported and ongoing AdCC clinical trials that target MYB.

In summary, the relationship between MYB expression and neuronal differentiation holds promise for therapeutic strategies using differentiation agents. To date these have not been particularly effective in clinical trials but it is notable that these are single-agent trials indicating that additional treatments should be used to target AdCC in patients.