**Fibrosis and metastatic uveal melanoma (mUM)**

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**Purpose:** Approx. 50% of UM typically metastasise to the liver, leading to a fatal outcome. The reasons for therapy resistance of mUM remain unclear, and hence all characteristics of mUM are being studied in detail, in order to disclose potential therapeutic targets. This includes the assessment of the mUM microenvironment, including their relationship to resident liver cells (e.g. hepatic stellate cells (HSCs)), reactive inflammatory infiltrates, and tumour-related fibrosis. Our previous data examining the secretome of primary UM indicated that hepatic fibrosis/HSC activation was amongst the most differentially upregulated biological process, suggesting that this is required during tumour progression.

**Methods:** 32 mUM samples underwent Gomori trichrome staining to highlight the extent and degree of collagen deposition (as a measure of fibrotic response) within and surrounding the metastases, and using immunohistochemistry for MelanA, BAP1, alpha-smooth muscle antigen (α-SMA) and CD68. Peri- and intratumoral fibrosis was scored independently by two pathologists (SEC, TS) as follows: 0 (not present), 1 (mild), 2 (moderate), 3 (severe). α-SMA cell positivity adjacent to- and within the mUM masses was also evaluated. The following features were also noted: hepatic location of mUM, cell type, necrosis, pigmentation, and presence of reactive inflammation.

**Results:** The examined mUM were predominantly of epithelioid cell type; 6 were spindle; and 2 mixed cell morphology. Necrosis was seen in 6 mUM. All mUM were positive for MelanA; most were nBAP1- with the exception of two tumours that were clearly nBAP1+. An intratumoural fibrosis score of 3 was a consistent feature in extensive and advanced hepatic mUM disease. Peri-tumoural fibrosis (scores 2 or 3) was a common feature of most mUM. In such cases, reactive lymphocytic infiltrates were outwith these fibrotic walls. α-SMA positive cells were observed both intra-tumourally and in a peri-tumoural distribution: those α-SMA+ cells at the tumour edge appeared to be activated HSCs; whilst those within the mUM were ‘fibroblast-like’.

**Conclusions:** Our research suggests that intratumoural fibrosis acts as a structural lattice, providing support for UM cell colonisation and growth. Peritumoural fibrosis in mUM acts as a fortification, possibly hindering drug and inflammatory cell penetrance. Future treatment strategies should take into account the tumour microenvironment.