**TNFR1 influences the proliferation and migration of Uveal Melanoma cells**

Sophie T. Gerstlauer1,2, Lachlan Ashby2,3, Janney Z Wang2, Thomas Grewal2, **Fanfan Zhou**2

Institute of Molecular Medicine, Faculty of Medicine, Martin Luther University1, Halle (Saale), Germany
Molecular Drug Development Group, Sydney Pharmacy School, The University of Sydney2, Sydney 2006, Australia;

School of Medical Science, The University of Sydney3, Sydney 2006, Australia.

**Background / Aims.** Uveal melanoma (UM) is the most common intraocular malignancy in adults and is associated with a poor prognosis. Metastasis develops in up to 50% of patients. Tumor proliferation and metastasis are influenced by inflammatory signals, such as tumor necrosis factor-alpha (TNFα), through its interaction with TNF receptor 1 (TNFR1) and TNFR2. However, the specific roles of TNFα and its receptors in UM cell proliferation and metastasis remain unclear. This study aims to investigate the impact of TNFR signaling on the proliferation and metastasis of UM cells.

**Methods.** Protein expression of TNFRs was evaluated by Western blotting in a panel of UM cell lines and primary cultures derived from patient tumors. TNFR knockdown was achieved using siRNA silencing in 92.1 and OMM2.5 cell lines, which originate from primary and metastatic tumors, respectively. Gene silencing efficiency was confirmed by Western blot analysis. Cell viability and proliferation were assessed using MTT assay and Incucyte® live-cell imaging. The metastatic potential of the tumor cells was evaluated using a transwell migration assay. Additionally, conditioned media from polarized macrophages (M0, M1, and M2 phenotypes), which contain TNFα, were applied to UM cells, and subsequent cell viability was assessed.

**Results.** Both TNFR1 and TNFR2 were found to be expressed in UM cell lines and primary cultures as well as non-tumor melanocytes. Silencing of TNFR1, but not TNFR2, led to increased cell viability and proliferation, along with reduced migration in both 92.1 and OMM2.5 cells. Conditioned medium derived from M1-polarized macrophages significantly reduced cell viability and proliferation, whereas media from M0 or M2 macrophages had no observable effect.

**Conclusion / Discussion.** TNFR1 inhibition appears to enhance proliferation while reducing the metastatic potential of both primary and metastatic UM cells, whereas TNFR2 does not exhibit a significant effect. Protein factors secreted by pro-inflammatory M1 macrophages, particularly TNFα, are potent in suppressing UM tumor cell growth. These findings suggest that TNFR1 plays an essential role in regulating UM tumor growth and metastasis, warranting further investigation into its potential as a pharmacological target.

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