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Role of Id3 in melanoma dedifferentiation and resistance to targeted therapy

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Melanoma is the deadliest form of skin cancer which is transformed from the melanocytes. Sunburn is one of the leading causes of melanoma. Patients acquire various mutations during melanoma pathogenesis which are responsible for the tumour progression, metastasis and invasion. Additionally, a subpopulation of melanoma cells is dedifferentiated due to the recapitulation of expression pattern also found in neural crest cells. Despite several targeted and immunotherapies have been approved for the treatment of metastatic melanoma, the gain of resistance reduces the efficiency of these drugs. A number of reports suggest the role of dedifferentiation in resistance to the therapies but the exact mechanism behind this is poorly understood. Therefore, in this study, a new protein was identified which plays role in dedifferentiation and resistance in melanoma cells.

In this project, it was shown that Id3 expression is upregulated in melanoma cells compared to the human melanocytes. Also, it was found that Id3 expression is higher in primary and metastatic melanoma patient samples as well as in dermal melanocytic nevus cells. By means of gain and loss of function studies, it was shown that Id3 alone does not alter the proliferation or cell cycle in melanoma cells. However, Id3 expression in melanoma cells promotes cellular migration. On screening a large set of melanoma associated genes it was revealed that Id3 expression is inversely proportional with the melanocyte differentiation marker gene-SOX10 and MITF.

It was also demonstrated that Id3 expression is upregulated in the BRAF and NRAS mutated cell lines upon treatment with vemurafenib and trametinib respectively. Also, from the expression analysis, it was shown that higher Id3 expressing cell lines after treatment with inhibitors display dedifferentiated phenotype. Further, I confirmed the role of Id3 expression in vemurafenib or trametinib resistance by showing that after knocking down or overexpressing Id3 in melanoma cell line sensitizes or confer resistant respectively to the treatments. These findings highlight the importance of Id3 in melanoma resistance against targeted therapy and inhibition of Id3 clinically in metastatic melanoma patients could increase the efficacy of the current treatment.