Phenotype switching in melanoma cells resistant to targeted therapy

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Melanoma is an aggressive malignancy that is, despite being a rare type of cancer, responsible for the vast majority of skin cancer-related deaths. Recent advances in melanoma therapy, like targeted therapy and immunotherapy, contributed profoundly to the increased overall survival of patients. Nevertheless, the development of resistance to therapy remains a major clinical issue. Targeted therapy, like the BRAF inhibitor (BRAFi) therapy for melanoma patients harboring the V600E mutation, is initially highly effective, but the majority of patients develop resistance and relapse within a few months.

To better understand the mechanisms of resistance to the BRAFi targeted therapy, we generated cell lines resistant to vemurafenib, a BRAF inhibitor used for the treatment of late-stage melanoma with the common BRAFV600E mutation. Vemurafenib-resistant human melanoma cell lines were generated by growing primary melanoma, WM793B cell line, and metastatic melanoma, A375M cell line, both harboring the BRAFV600E mutation, in the vemurafenib-enriched medium. The occurrence of resistance was confirmed by MTT assay. Newly generated resistant cell lines showed immense phenotype changes in terms of cell migration and proliferation. Our results indicated partial EM transition, which is known to increase invasive cell properties, promoting resistance to anti-cancer drugs. We performed mass-based parallel cell mRNA sequencing (RNA-seq) and found that the mechanism of resistance differs between the two cell lines. Furthermore, we have demonstrated a significant downregulation of metastasis suppressor genes, NME1 and NME2 and the p53 protein isoform Δ133p53β, which was shown to promote cancer cell invasion.

A number of previous studies suggested several mechanisms of resistance and phenotype switching in targeted therapy. Our results set a new direction for further research in therapy resistance that needs to be elucidated.