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The role of ERRFI1 in melanoma progression and resistance towards targeted therapy

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Melanoma is the most lethal type of skin cancer that originates from melanocytes. Targeted therapy, as one of the main therapeutic methods for melanoma, achieves great clinical efficiency at the beginning of treatment. However, drug resistance inevitably arises due to mechanisms such as the reactivation of the MAPK pathway. Our lab previously demonstrated that ERBB receptor feedback inhibitor 1 (ERRFI1), a neural crest-associated gene, is highly expressed in metastatic melanoma and correlates with poor prognosis. In this study, I validated that ERRFI1 expression was upregulated in melanoma and demonstrated that it positively correlated with AXL expression, but negatively correlated with SOX10 and MITF expression, as well as with melanocytic differentiation markers, including TYR, DCT, and MLANA. Downregulation of ERRFI1 increased the sensitivity of melanoma cells to vemurafenib (BRAF inhibitor). Furthermore, high ERRFI1 expression levels were found in BRAF inhibitor (BRAFi)-resistant cells. Loss of ERRFI1 resensitized BRAFi-resistant melanoma cells to vemurafenib.
Mass spectrometry-based proteomic analysis between ERRFI1 knockdown (KD) and control samples revealed that silencing ERRFI1 inhibited the reactivation of ERK and AKT signaling pathways, which usually contribute to promoting drug resistance. Furthermore, miR-200c was identified as a tumor-suppressive microRNA that targeted the 3' UTR of ERRFI1, resulting in its downregulation. This also resensitized BRAFi-resistant melanoma cells to vemurafenib. This study highlights the critical role of ERRFI1 in melanoma progression. These findings suggest that ERRFI1 is a promising therapeutic target for treating melanoma and offers potential strategies for overcoming drug resistance.