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"Stroma-induced phenotypic plasticity offers phenotype-specific targeting to improve melanoma treatment"

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Abstract

Cancer cells' phenotypic plasticity, promoted by stromal cells, contributes to intra-tumoral heterogeneity and affects response to therapy. We have disclosed an association between fibroblast-stimulated phenotype switching and resistance to the clinically used BRAF inhibitor (BRAFi) vemurafenib in malignant melanoma, revealing a challenge in targeting the fibroblast-induced phenotype. Here we compared molecular features and drug sensitivity in melanoma cells grown as co-cultures with fibroblasts *versus* mono-cultures. In the presence of fibroblasts, melanoma cells switched to the dedifferentiated, mesenchymal-like, inflammatory phenotype that showed reduced sensitivity to the most of 275 tested cancer drugs. Fibroblasts, however, sensitized melanoma cells to PI3K inhibitors (PI3Ki) and particularly the inhibitor of GSK3, AR-A014418 (GSK3i), that showed superior efficacy in co-cultures. The proteome changes induced by the BRAFi+GSK3i combination mimicked changes induced by BRAFi in mono-cultures, and GSK3i in co-cultures. This suggests that the single drug drives the response to the combination treatment, depending on fibroblast presence or absence, consequently, phenotype. We propose that the BRAFi and GSK3i (or PI3Ki) combination exemplifies phenotype-specific combinatorial treatment that should be beneficial in phenotypically heterogeneous tumors rich in stromal interactions.