

# Celecoxib Promotes Phenotype Switching in Cutaneous Melanoma Treated with Dabrafenib <sup>†</sup>

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**Abstract:** Cutaneous melanoma is a heterogeneous tumor with one of the most complex therapeutic resistance mechanisms described. Among them, invasive phenotype switching characterized by low MITF (microphthalmia transcription factor)/high AXL predicts early resistance to multiple targeted drugs in melanoma. Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, proved to be a valuable adjuvant in cutaneous melanoma in preclinical studies. The aim of our *in vitro* study was to evaluate how celecoxib impacts on treatment response of melanoma cells treated with dabrafenib. In particular, we tested for the first time if celecoxib could prevent phenotype switching in two human melanoma cell lines harboring *BRAF* mutation, A375 and SK-MEL-28. All *in vitro* experiments were carried out on A375 and SK-MEL-28 human melanoma cell lines, positive for *BRAF* mutation. After performing viability tests, cells were treated with a suitable dose of dabrafenib and celecoxib for 72 h. There were 4 groups of interest, as follows: group 1 - untreated cells, group 2 – dabrafenib 200 nM, group 3 – celecoxib 50 nM, group 4 – celecoxib 50 nM + dabrafenib 200 nM. Following different exposure regimens, cells were evaluated for cell death induction using flow cytometry (FACS) and membrane lysis by dosing lactate dehydrogenase (LDH). The expression of key proteins involved in phenotype switching was dosed via WB: transforming growth factor-beta (TGF- $\beta$ ), MITF, AXL, Yes1 associated transcriptional regulator (YAP1), TAZ, COX-2, and tyrosinase. Celecoxib enhanced the apoptotic effect of dabrafenib in each melanoma cell line compared to dabrafenib group ( $p < 0.0001$ ). Even so, celecoxib promoted MITF low/AXL high expression in A375 and SK-MEL-28 cell lines ( $p < 0.0001$ ). Celecoxib induces phenotype switching in cutaneous melanoma *in vitro*. This is an important finding limiting the *in vivo* use of celecoxib as an adjuvant in melanoma.

**Keywords:** melanoma; celecoxib; dabrafenib; MITF; AXL.

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## **Conflicts of Interest**

The authors declare no conflict of interest.