High mitochondrial mass identifies a subpopulation of vemurafenib-resistant cancer stem cells in melanoma

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Drug resistance still represents the main reason for therapy failure in melanoma patients. In this regard, cancer stem cells (CSCs) are thought to be responsible for treatment evasion and tumor relapse. Here, we used A375 and WM115 human melanoma cells to dissect the role of mitochondria in conferring the drug-resistant CSC phenotype. More specifically, we conducted flow cytometry analysis to fractionate this cell line into ABCG2+ (stem-like) and ABCG2- (non-stem) subpopulations: interestingly, ABCG2+ cells exhibited higher mitochondrial mass. Likewise, A375 and WM115 melanospheres, known to be enriched in ABCG2+ CSCs, showed enhanced mitochondrial content. In particular, an increase in mitochondrial biogenesis (PGC1-α protein levels), OXPHOS (complex I-V protein levels) and fusion (OPA1 and MFN2 protein levels) was found in spheroids with respect to the parental cell line, leading to a metabolic switch towards an oxidative phenotype characterized by higher oxygen consumption, ATP synthesis and ROS production. Notably, PGC1-α silencing led to the suppression of sphere formation and ABCG2 enrichment. Similarly, SR-18292 and XCT790, two PGC1-α inhibitors, were able to block melanosphere propagation and ABCG2+ cell proliferation. In summary, increased mitochondrial content is associated with a vemurafenib-resistant stem-like phenotype in melanoma, and therapeutically targeting the mitochondria-enriched CSC subpopulation might overcome drug resistance.