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Knockdown of Hypoxia-Inducible Factor-1α Improves the Efficacy of Doxorubicin in B16.F10 Murine Melanoma Cells †

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Abstract: In cancer, it is unequivocally established that apoptosis is an efficient roadblock by efficiently removing transformed cells. However, our team and others showed that oncogenesis re-appropriates apoptosis and its effectors (mainly caspases) to fuel certain of its hallmarks, such as cancer cell invasion. Indeed, our team showed recently that low-level caspase activation in the so-called failed apoptotic cells is compatible with survival and promotes melanoma aggressiveness. Using a sensitive caspase activation reporter, we isolated and thoroughly characterized melanoma cancer cells surviving the induction of apoptosis. Importantly, our results suggest these cells have a particular transcriptomic signature associated with cellular motility. In line with this, cells surviving apoptosis gain aggressiveness: they have an increased migration and invasion potential both *in vitro* and *in vivo*. We further demonstrate that failed apoptosis-associated gain in invasiveness is regulated by the JNK pathway, while its transcriptomic signature can discriminate primarily from metastatic human melanoma tumors. In a complementary study, we tested whether caspase-3 has a protease-independent function in melanoma cell motility. We now have preliminary data that caspase-3 but not caspase-7 is required for melanoma cell migration and invasion since its downregulation impairs chemotaxis, collective migration, and invasion. In addition, caspase-3 IP-MS proteomic analysis revealed that most putative interacting proteins are associated with the actin cytoskeleton. To take this study further, we now perform several proteomic assays, such as BioID, to establish how and where exactly caspase-3 interferes with melanoma cell motility.

Keywords: oncogenesis; caspase-3; melanoma cells.

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Conflicts of Interest

The authors declare no conflict of interest.