BIOLOGICAL EFFECT OF IRISIN IN IN VITRO MODELS OF METASTATIC MELANOMA CELLS

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Melanoma is an aggressive type of tumour that mainly occurs on the skin, with poor prognosis for patients with metastatic disease (brain and bones). Recent studies showed that irisin affects signaling pathways in several types of cancer. Irisin is a newly discovered 12kDa messenger protein, as part of the fibronectin type III domain containing 5 (FNDC5), involved in energy metabolism and Musculo-skeletal homeostasis. The biological properties of irisin on metastatic melanoma (MM) have not been described yet. We explored the biological effects of recombinant irisin (r-irisin) in *in vitro* models of MM cells ($HBL^{wt/wt}$, $LND1^{wt/wt}$, $Hmel1^{V600K/wt}$ and $M3^{V600E/V600E}$) harbouring oncogenic activation of BRAF. We treated MM cells with different concentrations of r-irisin (10nM, 25nM, 50nM, 100nM) for 24h-48h. MTT-assay highlighted that r-irisin didn't affect the proliferation of MM cells. We subsequently treated MM cells with 10nM r-irisin, corresponding to the dose of r-irisin reported to exhibit biological activity *in vitro*. Chemoinvasion-assay showed that r-irisin reduced the metastatic potential of $HBL^{wt/wt}$ (12%) and $LND1^{wt/wt}$ cells (40%, $p<0.05$), but didn't affect the invasion of $BRAF^{mut}$ cells. These results were supported by gelatin zymography analysis showing a reduction of the enzymatic activity of MMP2 and MMP9 in $BRAF^{wt/wt}$ cells treated with 10nM r-irisin. Moreover, gene expression analysis (qPCR) of invasion markers MMP2 and MMP9 and of the fibrinolytic system (uPAR, uPA and PAI-1) highlighted a crucial role of 10nM r-irisin treatment in the inhibition of proinvasive systems in $HBL^{wt/wt}$ and $LND1^{wt/wt}$. In conclusion, our results suggest a selective possible role of 10nM r-irisin in preventing the metastatization of $BRAF^{wt/wt}$ melanoma. Further studies will be directed to explore r-irisin in association with vemurafenib in MM $BRAF^{mut}$ cells.