EFFECT OF IRISIN ON uPA/uPAR SYSTEM 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. Several proteins with proteolytic activity mediate the interaction between melanoma cells and the tumor microenvironment. In particular uPA (urokinase-type plasminogen activator) and its receptor uPAR and gelatinase (MMP-2 and MMP-9) orchestrate melanoma spreading towards the surrounding extracellular matrix (ECM) until the formation of distant metastases. 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. Recent studies also showed that irisin reduced the invasion capability of several types of cancer cells, however the effect of irisin on melanoma cells has not been described yet. We treated four metastatic melanoma cell lines 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 $HBL^{wt/wt}$ and $LND1^{wt/wt}$ cells ($p<0.05$), but didn't affect the invasion of $BRAF^{mut}$ cells ($Hmel1^{V600K/wt}$ and $M3^{V600E/V600E}$). Gelatin zymography analysis showed a reduction of MMP-2 and MMP-9 enzymatic activity in $BRAF^{wt/wt}$ cells compared to untreated cells. Moreover, gene expression analysis (qPCR) of MMP-2 and MMP-9 and of the fibrinolytic system (uPAR, uPA and PAI-1) highlighted a significant reduction of pro-invasive systems ($p<0.01$) in $HBL^{wt/wt}$ and $LND1^{wt/wt}$ cells treated with 10nM irisin compared to untreated cells. In conclusion, our results highlighted that irisin impaired the pro-invasive systems of $BRAF^{wt}$ melanoma cells rather than $BRAF^{mut}$, suggesting a possible role of irisin in reducing $BRAF^{wt}$ melanoma cells invasion potential.