ANTIMETASTATIC EFFECT OF A NOVEL NON COMPETITIVE CXCR1/CXCR2 INHIBITOR IN HUMAN MELANOMA

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CXCL8 and its receptors (CXCR1/ CXCR2) are recognized to contribute to the tumor growth and metastasis progression in human malignant melanoma.

Aim of this study was to evaluate the potential antimetastatic effect of meraxin, a novel non competitive allosteric inhibitor of CXCR1 and CXCR2.

Human melanoma cell lines (M20 and A375SM) with different cell surface expression of CXCR1 and CXCR2 were used for *in vitro* and *in vivo* studies. Meraxin, at the concentration range of 10^{-10}-10^{-6}M, significantly suppressed, in a concentration-dependent manner, *in vitro* invasion, migration and proliferation properties of M20 and A375SM.

The effect of meraxin on *in vivo* tumor growth and on the capacity of melanoma cells to form spontaneous and artificial lung metastases was investigated both macroscopically and microscopically in CD-1 nu/nu mice. Oral treatment with meraxin 8 mg/kg significantly prevented the lung artificial metastases induced by intravenous injection of M20 and A375SM ($p<0.01$ and $p<0.05$, respectively). The protective effect of the compound was confirmed on intramuscularly M20-induced spontaneous lung metastases. In fact, meraxin (8 mg/kg) effectively reduced metastatic nodules, if the treatment started when the tumor was palpable; this effect was dose-dependent. The antimetastatic activity of meraxin was not due to its cytotoxic effect on the tumor cells because A375SM and M20 cells proliferated normally and did not activate the apoptotic program when exposed to meraxin *in vitro*. In addition, in order to confirm the selectivity of the compound, human melanoma SbCl1 cell line, not expressing CXCR1 and CXCR2, was used. As expected, SbCl1 cells were found to be unresponsive to meraxin treatment in terms of *in vitro* cell proliferation and migration, and *in vivo* metastatization. Unlikely to the antimetastatic effect, local growth of melanoma tumors was not affected by meraxin.

In conclusion, our results demonstrated, for the first time, that the inhibition of CXCR1 and CXCR2 has a potential antimetastatic activity, prospecting the clinical potentiality of CXCR1/CXCR2 antagonists, such as meraxin, in the therapy of metastatic melanoma.