The effect of histamine antagonists on human melanoma malignum progression in SCID mice

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Malignant melanoma is a skin tumour with a very high mortality rate, and the incidence of this tumour is increasing rapidly throughout the world. Consequently it stimulates a plethora of in vitro and in vivo research, modelling melanoma growth on one hand and searching for effective drugs for possible human therapy on the other.

Melanoma cells and tissue but not melanocytes contain significant amounts of histamine and histidine decarboxylase (HDC), the enzyme responsible for the synthesis of histamine, and express histamine receptors. The functional significance of histamine was examined using specific antihistamines in vitro and in vivo in the human melanoma cell line HT168 and severe combined immunodeficiency (SCID) mice.

It was shown that the H2 receptor antagonist cimetidine when combined with N,N-diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine-HCl (DPPE), a tamoxifen derivate, inhibits the proliferation of HT168 cells. Furthermore, it is suggested that there are factors that inferfere with the growth of HT168 cells xenografted to immunodeficient mice, and cimetidine and DPPE together may significantly influence these factors. This combination of antihistamines also increases the survival of human melanoma-grafted mice. Ranitidine alone evokes a weaker and more transient inhibition in tumour growth.

These changes are accompanied by enhanced infiltration of interferon-γ-producing mouse macrophages into the tumour tissue. These findings suggest that two different mechanisms are probably acting concordantly: direct inhibition of tumour cell proliferation by the H2 receptor antagonists, and activation of the local immune response characterized by interferon-γ production. These findings may help to elucidate the possibility of a rationally designed antihistamine strategy in melanoma therapy.