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Matrix Metalloproteases and Cell Motility in Malignant Mesothelioma

Av

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ABSTRACT

Invasion and metastasis of malignant tumor cells requires destruction of and migration through extracellular matrix (ECM) such as basement membrane and interstitial stroma. The ECM-degrading proteases produced by tumor cells and stromal cells and cell motility play a crucial role in this process.

Malignant mesothelioma is an asbestos-associated and highly aggressive tumor arising from mesothelial cell-lined surfaces of body cavities. It is most often present in the pleural cavities. The resulting tumor often forms diffuse thickening of involved surfaces rather than solitary rounded lesions seen in other neoplasms. Malignant mesotheliomas invade and spread through the underlying basement membrane or along serosal surfaces. Metastases occur in up to 75 % of mesothelioma patients. There is no effective and standard treatment for malignant mesothelioma.

The general aim of this thesis is understand why malignant mesotheliomas invade surrounding tissues and metastasize. Using human malignant mesothelioma cell lines as a model, the goal of this thesis was to: (i) investigate expression and production of MMPs in malignant mesothelioma cells. All investigated mesothelioma cell lines expressed mRNA for MMP-1, MMP-2, MMP-3, MMP-9 and 6/8 cell lines expressed MMP-7, 3/8 cell lines expressed MMP-10. MMP-11 was not detected in any of mesothelioma cell lines tested. MMP -2 and MMP -9 produced by mesothelioma cells degraded gelatin, whereas MMP -3 degraded laminin, fibronectin and vitronectin; (ii) the exposure of malignant mesothelioma cells to different growth factors, including epidermal growth factor (EGF), transforming growth factor- α (TGF- α), amphiregulin (AR), heparin-binding EGF-like growth factor (HB-EGF), β -cellulin (BTC), stem cell factor (SCF), insulin-like growth factor (IGF)-I, II, acidic-fibroblast growth factor (aFGF), basic FGF (bFGF) and hepatocyte growth factor (HGF), increased production of MMP-9 and/or MMP-3. Production of MMP-2 was not affected by any growth factors used in this study; (iii) examine the cell motility (chemotaxis and chemokinesis) induced by multiple growth factors in malignant mesothelioma cells. The growth factors such as EGF, TGF- α , AR, HB-EGF, BTC, IGF-I, IGF-II and SCF stimulated chemotactic and/or chemokinetic motility in mesothelioma cells tested, whereas none of aFGF, bFGF, granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6) induced migration in the same mesothelioma cells; (iv) study the role of novel EGF receptor-tyrosine kinase (EGFR-TK) inhibitors (ZD1839, OSI-774, CI-1033) on cell proliferation and invasive behaviour of malignant mesothelioma *in vitro*. All three drugs inhibited TGF- α induced cellular proliferation, cell migration (chemotaxis) and the production of MMP-9 in three cell lines tested.

In conclusion, we have described the expression, production and regulation of MMPs in malignant mesothelioma cells. In addition, our results indicate that MMPs may play a role in malignant mesothelioma cell invasion. Furthermore, cell motility induced by different growth factors may contribute to the highly invasive behaviour of malignant mesothelioma. We have also demonstrated EGFR-TK inhibitors inhibit the proliferation, migration and MMPs production in malignant mesothelioma cells suggesting that these drugs may become an effective treatment strategy for malignant mesothelioma.

Keywords: matrix metalloproteases (MMPs), cell motility, growth factors, malignant mesothelioma, invasion

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