PTPμ, a prognostic indicator for secondary bone metastasis in human ductal breast cancer

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Introduction: Protein tyrosine phosphates (PTP’s) consist of a large family of related enzymes. They play a major role in many cellular functions including cell survival, proliferation, differentiation and motility. The protein family is also actively involved in the skeletal development and metabolism. Certain forms of PTPs has been shown to be potential target for bisphosphate in the treatment of bone metastasis from cancer. It is well established that dysregulation of these pathways is implicated in cancer development and progression. The receptor like protein tyrosine phosphate (PTPμ) has a similar structure to cell to cell adhesion molecules and has been shown to exhibit homophilic binding and confer cell-cell adhesion in cells including epithelial and cancer cells. Like all the PTP’s PTPμ it is regulated by the balance between the actions of protein tyrosine kinase (PTK) and protein tyrosine phosphate (PTP). PTPμ which is located on the cells surface regulates the phosphorylation of the E-cadherin adhesion molecule which control the function of cadherin, a transmembranous adhesion molecule. If there is a reduction in cadherin function there is a reduction in cell adhesion and in the presence of cancer this allows the separation of metastatic cells from the primary tumour. There has been no prior study in linking the expression of PTPs in primary cancers and the tendency for bone metastasis. In this study we examine human ductal breast cancer tissue to see whether PTPμ could be a positive predictor for metastatic spread and specifically skeleton metastasis.

Materials and Methods: PTPμ transcripts were assessed in fresh frozen sections in adjacent non-malignant ‘normal’ ductal breast tissue and ductal breast carcinoma (normal breast, n = 23; ductal carcinoma, n = 72) using real time quantitative polymerase chain reaction (PCR). The results were normalized against the normal epithelial marker and analysed in relation to the tumour grade, the Tumour, Node and Metastasis (TNM) stage and the Nottingham Prognostic Indicator (NPI), and the clinical outcome over a 10 year period (Table 1). The localization of PTPμ in the tissues was assessed using immunohistochemical staining.

Results: PTPμ was found in both normal mammary epithelial tissue and ductal breast cancer cells. The degree of staining was, however, markedly weaker in the cancer cells (figure 1). Using quantitative analysis, we have shown that the PTPμ levels are lower in breast cancer tissue compared to normal tissue. PTPμ were found in significantly lower levels in tumours from patients who developed metastases (p=0.019) when compared with patients who remained disease free. Looking specifically at skeletal metastasis PTPμ had lower transcript levels (p=0.071) compared to normal tissue (figure 2) and if we looked at the combined group of who suffering a metastasis there is a significant reduction in transcript numbers (p=0.034). No significant correlation was seen between the different grades, TNM stages or NPI.

Discussion: Previous studies looking at the different PTP have, in general, indicated that breast cancer is associated with an increase in the PTP expression. This finding is not universal as Zheng et al. showed that the transmembranous PTPγ was more highly expressed in normal tissue than in breast tumour cell lines. PTPμ appears to have a similar tumour suppressing role and here for the first time we have found that in ductal breast cancer there is a significant reduction in transcript levels in cases of generalized and skeletal metastasis. These finding may be potential useful for clinical practice and be potential new therapeutic targets.

References:

Table 1: Clinical information of the study cohort (n= 73).

Figure 1: Immunohistochemical staining of PTPμ showing ductal breast cancer tissue on the left aspect of the slide and normal ductal breast tissue on the right at magnification x4 with inserts at magnification x40

Figure 2: Comparisons between patients who remained disease free and those who developed skeletal metastasis and either skeletal or general metastases