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Thesis abstract

Role of Progesterone Receptor Membrane Component 1 (PGRMC1) in cancer cell biology

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Progesterone Receptor Membrane Component 1 (PGRMC1) is a 22 kDa Cytochrome b5 related haem-binding protein. PGRMC1 is an evolutionarily conserved protein. It is involved in maintaining various cellular processes such as damage resistance, lipid and drug metabolism, apoptosis and cell proliferation. PGRMC1 is over expressed in multiple types of cancer. It plays an important role in cancer by regulating tumour growth and cell differentiation. A previous proteomics study on human breast cancer tissue found that PGRMC1 was phosphorylated. Three different isoforms of PGRMC1 were identified and phosphatase treatment revealed those isoforms were differentially phosphorylated. PGRMC1 protein contains putative Serine and Tyrosine phosphorylation sites and has binding sites for Src homology 2 (SH2) and SH3 domain containing proteins. In this thesis, I investigated the role of phosphorylated PGRMC1 in cancer cell biology and tumourigenesis. I generated mutant stable cell lines by removing putative phosphorylation sites at Serine and Tyrosine residues of PGRMC1. Removal of phosphorylation sites in the Mia PaCa-2 pancreatic cancer cell line, affected the cell biology profoundly. It induced changes in cellular proteome and signalling pathways. It changed cell morphology and migration patterns, induced mesenchymal to amoeboid transition. It affected glucose uptake and lactate production. Overexpression of wild type PGRMC1 showed more cancer relevant phenotype. Depletion of PGRMC1 by RNA interference and removal of Serine phosphorylation sites impaired MDA-MB-231 breast cancer cell's metastatic growth in a mouse xenograft model. Overexpression of PGRMC1 increased breast cancer bone metastases and induced osteolytic bone damage. Taken together, these results suggest that PGRMC1 is involved in tumourigenesis and a potential target for cancer therapeutics.

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