



Master's Thesis
Drug Discovery and Development (MSc)
Faculty of Biomedicine
University of Turku, May 2018

Role of PIM kinase-mediated regulation of Notch3 receptor protein in breast cancer

Author: William Eccleshall

Abstract

The proviral integration site for Moloney murine leukaemia virus (PIM) kinase family and the Notch receptor protein family are known to regulate certain human malignancies and have therefore become attractive targets for drug development in recent years. Interestingly, interactions between PIM1 and Notch1 have recently been highlighted as a potential driving force behind breast and prostate cancer cell signalling. However, while Notch1 is generally believed to play an oncogenic role in certain cancers, the function of Notch3 is less clear with conflicting reports on its influence in different types of cancer.

In this project *in vitro* kinase assays provided evidence that Notch3 is phosphorylated by PIM1 at S1673. Subsequently, analysis performed with fluorescence microscopes determined that this enzyme-substrate relationship is highly likely to exist in MCF-7 cells. Moreover, *in silico* analysis of gene expression in patient tumour samples and Western blotting of MCF-7 cell lysates suggest that the two share a close expression pattern in breast cancer. In functional terms, Notch and PIM were found to promote viability and metabolism in these cells while further experiments linked Notch3 to proliferation, adhesion and cell structure.

The precise downstream signalling events which follow PIM-mediated phosphorylation of Notch3 remain unclear. Nonetheless it is hoped that the results presented here will enhance understanding of the role of PIM kinases and Notch receptors in breast cancer and inspire targeted approaches towards breast cancer treatment.