Triple-negative breast cancer

THE PIM1 KINASE SHOWS GENOME DRIVEN UPREGULATION, SUPPRESSES APOPTOSIS, ENABLES COLONY FORMATION AND CELL MIGRATION AND IS A POTENTIAL TARGET IN TRIPLE-NEGATIVE BREAST CANCER

F. Brasó Maristany, A. Grigoriadis, E. Noël, P. Gazinska, E. de Rinaldis, S. Pinder, P. Marks, A. Tutt
Research Oncology Department - Cancer Division, King's College London, London, UNITED KINGDOM

Background: Triple-negative breast cancers (TNBCs) are aggressive, associated with poor prognosis and lack targeted therapies, mainly due to the absence of suitable molecular targets. Subgroups have evidence of MYC amplification and upregulation. MYC is a known driver of malignant cell proliferation but also drives apoptosis if not controlled by other mechanisms. Synergistic effects between MYC and the PIM1 kinase on tumourigenesis have been shown in other cancers. PIM1, located on 6p21-p25, is frequently gained in TNBCs and is involved in cell proliferation, migration and suppression of apoptosis. This study focused on the role of PIM1 as an oncogenic driver and suitable therapeutic target for TNBCs, especially in those with MYC upregulation.

Methods: To identify copy number gained and upregulated genes in TNBC, genomic and transcriptomic profiling of 138 fresh frozen breast cancers (107 TNBC) was conducted using Affymetrix SNP6 and Human1.0ST arrays in conjunction with the analysis of publicly available datasets. Using RNAi, PIM1 was knocked down in non-malignant and breast cancer cell lines (BCCL) to assess its influence on cell proliferation, apoptosis, colony formation and cell migration.

Results: Genomic profiling confirmed an increased PIM1 expression in TNBC compared to non-TNBC tumours (1.5fold, P value <0.001), which correlated with its copy number levels (Cor 0.5, P value <0.001). High correlation between PIM1 gene expression and MYC amplification was also observed (P value =0.0015). In BCCLs, PIM1 expression was significantly higher for basal-like than luminal lines. PIM1 knockdown decreased cell growth and clonogenic ability in BCCLs with high PIM1 abundance and MYC amplification, while no effect was observed in BCCLs with lower PIM1 expression or in the non-malignant HMEC cells with high PIM1 but lacking MYC amplification. Upon PIM1 silencing, an increased caspase activity, reduced BAD phosphorylation and BCL2 protein levels were detected, as well as the ability to migrate was restricted as observed by transwell assays.

Conclusion: PIM1 is a keyplayer in TNBC tumorigenesis by protecting malignant cells from apoptosis, including that driven by MYC, and by supporting cell migration. Our results provide evidence for this kinase to be a potential therapeutic target for certain groups within TNBC.

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