Expression2Kinases (E2K) analysis identifies potential drugable kinases for targeted treatment of cervical carcinoma


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Aim/Background: Previous studies have implicated somatic mutations in PIK3CA, PTEN, STK1, MAPK1, ERBB2 and KRAS as well as several copy number alterations in the pathogenesis of cervical carcinomas. Although some of these mutations are potential targets for treatment they remain infrequent events. Single gene mutations are an important cause of pathway disruption, but there are many other factors implicated in pathway (in)activation (such as altered gene expression, gene interactions, effects of miRNAs, methylation, etc.) that may be of functional importance. We therefore used a different approach, gene set enrichment and pathway analysis, to unravel the major signaling networks that are common in most cervical cancer patients and could be drugable.

Methods: Four publicly available gene expression data (i.e. GSE5787, GSE7803, GSE9750 and GSE7410) were retrieved (9 cervical cancer cell lines, 39 normal cervical samples and 111 cervical cancer samples). One data set (i.e. GSE7410) was set apart for validation purposes. Validated biomarkers were interrogated using gene set enrichment analysis (GSEA) and Expression2Kinases (E2K) to delineate the driving signalling network.

Results: GSEA showed that the pathways with most genes involved were cell cycle, DNA replication, mRNA splicing, purine metabolism, E2F transcription, pyrimidine metabolism, direct p53 effectors, Aurora B signalling, PLK1 signaling events, and Fanconi anemia pathway. E2K identified a protein-protein interaction (PPI) network of 162 nodes and 20 drugable kinases: CDK1, CDK2, ABL1, ATM, AKT1, MAPK1, MAPK3, TRRAP, MAPK14, GSK3B, CSNK2A1, MAPK8, ATR, TAF1, HIPK2, TRRAP, PRLDC, CSNK2A2, RP56KA2, CD7, RP56KA1. This implicates that drugs such as olaparib, veliparib, imatinib, dactolisib, buparlisib, copanlisib, iparlisib, etc have the potential to be effective in the treatment of cervical cancer.

Conclusions: The potential targets for systemic treatment of advanced cervical cancer identified in this study should be considered as hypothesis raising. Further detailed in vitro and in vivo studies, linking genotype to phenotypes, are necessary to explore the effectiveness of manipulating the interesting pathways we proposed.

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