Proteomics as tool to identify therapeutic targets in cancer

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Understanding of pathways in cancers is more important than alterations at the DNA levels in individual genes. Activity of many pathways can be assessed by studying the proteome and the phospho-proteome. This is because the large majority of activated kinases can be rapidly identified owing to an increase in their auto phosphorylation activity and the corresponding pathways can be determined by looking at the profile of the kinases and their substrates that are phosphorylated. To date, 28 kinase inhibitors have been approved by FDA for cancer therapy. Identification of imatinib, a small molecule inhibitor against BCR-ABL tyrosine kinase, by Druker and colleagues revolutionized the treatment of patients with CML. Other examples include erlotinib and gefitinib targeting EGFR in non-small cell lung cancer and Trastuzumab in HER2 positive breast cancer. Given the central role of protein kinases in cell signalling networks and their potential as excellent therapeutic targets, phosphoproteome profiling to identify activated kinase pathways is an ideal approach to meet this goal. However, limited effort has been made to identify potential therapeutic targets in head and neck squamous cell carcinoma (HNSCC). Despite advances in clinical management, 5-year survival in patients with late-stage head and neck squamous cell carcinoma (HNSCC) have not improved significantly over the past decades. Consumption of tobacco continues to be one of the major established etiological factors in the pathogenesis of HNSCC. The practice of using smokeless tobacco (chewing tobacco) is more common in the socio-economic section of southern Asia particularly in India, accounting for 80% of global tobacco chewers. Prolonged tobacco chewing has been associated with the development of oral cancer. However, the molecular mechanism of the action of smokeless tobacco has not been understood. Hence, it is both necessary and essential to establish a cellular model which mimics the chronic in vivo tissue exposure to chewing tobacco. Our cellular model indicates that chronic exposure to chewing tobacco induces cellular transformation and also induces the expression Stearoyl-CoA desaturase (SCD). Inhibition of SCD resulted in decreased cellular growth and invasive abilities across a panel of head and neck squamous carcinoma cell lines. Tyrosine kinase signalling pathways are important for cellular processes and are shown to be deregulated in cancer; we sought to assess these pathways in HNSCC to look for potential therapeutic targets. We carried out phosphotyrosine profiling using a panel of HNSCC cell lines and compared it to a non-neoplastic cell line to identify activated tyrosine kinase signalling pathways in HNSCC. A number of tyrosine kinases were found to be differentially phosphorylated in HNSCC cell lines. One of these hyper phosphorylated kinases, DYRK1A, was shown to be important in tumorigenicity of aggressive HNSCC. Overall, our global phosphoproteomic findings confirm the high heterogeneity in the activation status of tyrosine kinase pathways across HNSCC and our approach presents an attractive means of identifying important therapeutic targets, such as DYRK1A. Taken together our results indicate that mass spectrometry is a useful tool to identify not only molecular signatures of carcinogen exposure but also molecules which can serve as novel therapeutic targets.

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