

Molecular Targets for Cancer Therapeutics: Insights from Genomic Aberrations and Protein Interactions

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Abstract

Cancer is a major health concern in both developed and developing countries. Lack of knowledge of underlying mechanisms leading to cancer, is one of the reasons responsible for absence of effective medication with least side effects. Adding to complexity of the situation, any two cancer patients will not respond in a similar manner to same treatment due to different molecular signature of aberration that lead to cancer. This is a major motivation driving the research in the area of personalized medicine. Large numbers of cancer-genomics projects like The Cancer Genome Atlas (TCGA) and Genomics of Drug Sensitivity in Cancer (GDSC) provide a wealth of information at multi-omics level. Machine learning-based models trained on multi-omics data and clinical health record of thousands of patients has a potential to a) identify all possible set of molecular aberration signature responsible for each cancer type and b) correlate these aberration signature to drug-response prediction. In this thesis, an attempt has been made to leverage the technology of deep- and machine learning to identify genomic aberrations that could serve as potential therapeutic target or prognostic/diagnostic biomarkers that could aid in prediction of survival-prognosis and drug response of patients in clinical settings. In addition to use of available data to bridge the gap between research and clinical practices, our laboratory group is actively involved in encouraging the use of compounds, extracted from natural sources like 'Ashwagandha' and 'honeybee propolis', in cancer treatment by studying the underlying mechanism of its anti-cancer activity specific to cancer cells only. Withanolides (secondary metabolites of Ashwagandha) and CAPE (bioactive component of honeybee propolis) have a very impressive anti-cancer pharmacological profile due to their reported properties like anti-metastatic, anti-apoptotic, anti-stress, anti-oxidant, anti-inflammatory and anti-angiogenic activity. In light of the reported activities of these natural compounds and pathways dysregulation reported in cancer cells with respect to their normal counterparts, an attempt has been made in this thesis to link this information to identify possible pathways affected by these compounds. The identification of pathways were followed by exploring the possible target protein to find the action mechanism behind specific activity of these natural compounds using bioinformatics and experimental approaches. This kind of basic research on unveiling the interactions and mode of action of these natural compounds with their target proteins and their resultant effect on pathways in cancer cell and normal cells, will aid in promoting the use of natural compounds in clinical practices in the long run.