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Leveraging OncoMD to identify synthetic lethal interactions between recurrently mutated genes

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Abstract

Most cancer therapies perform within a narrow therapeutic window causing numerous side effects and reducing the quality of life of cancer patients. Therefore, there is a need to develop new anti-cancer therapies of superior efficacy and minimal normal tissue toxicity. For this, identifying highly effective targets, which are essential for the survival of cancer cells, is required. A powerful genetic strategy in anticancer drug discovery is the exploitation of synthetic lethal interaction between genes. Synthetic lethal interaction is defined as interaction between two co-essential genes, in which inhibiting the function of either genes individually does not impact survival, but loss of function of both genes results in cell death. Cancer cells carry large number of mutations in many genes. These mutations can be grouped into gain-of-function, loss-of-function and function of unknown significance. Both gain and loss-of-function mutations occur in driver genes which are essential for cancer cells to grow and survive. MedGenome has built a database of somatic mutations – "Oncology Mutation Database" (OncoMD) by capturing data from published papers and public databases. We analyzed 2.2 million unique mutations in OncoMD and identified cancers in which certain mutation pairs occur more frequently than expected by chance. Analysis of these mutation pairs revealed well characterized genetic interactions between oncogenes and tumor suppressor genes and novel interactions that require further characterization. In conclusion, our analysis identifies cancer-specific susceptibilities that can be exploited for discovering novel drug targets.

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