Synthetic Lethal Targeting of Mismatch Repair Defective Cells

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Technology description

Synthetic Lethal Targeting of Mismatch Repair Defective Cells for Cancer Treatment
Researchers in the Department of Molecular Biology at Princeton University have developed a yeast-based high throughput chemical synthetic lethality screen to identify clinically relevant small molecules. Its application has led to the discovery of clinically approved drugs with previously unknown capacity to kill or selectively inhibit the growth of mismatch repair defective cells.
Mismatch repair is a highly conserved DNA repair pathway that plays a key role in maintaining genomic stability and the fidelity of genetic material. Mutations in genes involved in the mismatch repair pathway are implicated in many types of cancer, both hereditary and sporadic. For instance, colorectal cancer is the second leading cause of cancer deaths in the United States, and defects in DNA mismatch repair due to mutations in mismatch repair genes, including MSH2 , play a key role towards the development of 20% of hereditary and sporadic colorectal cancers. However, there are no treatment strategies or specifically designed drugs to target cancers with defective or inactivating mutations in mismatch repair pathways.
Loss of mismatch repair also plays a role in the development of chemoresistance, a primary challenge in medical treatments for conditions ranging from cystic fibrosis to cancer. Chemical synthetic lethality is an emerging strategy for specifically targeting cells with cancer-driving mutations. Because mismatch repair deficient tumors accumulate mutations at a high rate and become heterogeneous, targeting the variety of potential pathways altered in these cancer cells is challenging. Therefore, targeting the primary vulnerability is a rational approach for a broad-spectrum treatment.
Key Words
Mismatch repair, high throughput screening, drug design, drug discovery, pharmaceuticals, cancer, chemotherapy, anticancer therapeutics, chemical synthetic lethality, yeast

Advantages

· Design novel therapeutics to target cancers with mismatch repair defects
· Discover small molecules and pharmaceuticals to target mismatch repair defective cells

· Identify single gene and polygenic resistance targets
· Personalized cancer therapeutics
· Rapid, robust high throughput screen
· Inexpensive approach
· New use for existing drugs
· Selectively inhibit growth and viability of mismatch repair cells while leaving normal cells unharmed
· Larger therapeutic window than traditional chemotherapies

Institution

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