Selecting and Optimizing Cancer Therapy with Cell-Cycle Inhibition

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Technology description

The cytotoxic agents used in most current cancer therapies can kill cancer cells, but they do not prevent them from dividing. Cancers such as multiple myeloma remain fatal due to its rapid expansion of cancer cells and aggressive tumor growth during relapse. Researchers at Weill Cornell Medical College have developed an effective cell cycle-based combination cancer therapy that both prevents tumor cell replication and induces synergistic killing of tumor cells.

Cyclin-dependent kinase (Cdk)4 and the closely related Cdk6 are essential for the control of cell cycle reentry and progression through G1 phase of the cell cycle. Aberrant expression of Cdk4 and Cdk6 is a hallmark of cancer. In studies with CD-138 positive myeloma cells isolated from bone marrow from individual multiple myeloma patients with the orally-active selective Cdk4/6 inhibitor currently in clinical trials, PD 0332991, these investigators found that such cells were kept from dividing, but were not killed. However, the combination of this Cdk4/6 inhibitor with a cytotoxic agent effective in the patient's cells, delivered in a specific sequence, can both effectively stop cell division and kill tumor cells at reduced dose. Hence, they have developed an effective therapeutic method as well as a novel ex vivo cell culture system that recapitulates tumor cell drug sensitivity and resistance in the patient and can help identify the best cytotoxic agent and its appropriate dosage for a given patient. The various cytotoxic agents they have tested include several proteasome inhibitors (e.g. bortezomib, carfilzomib) and other common cancer therapies (e.g. cytosine arabinoside, dexamethasone).

Their research indicates that prolonged inhibition of cell cycle progression through G1 disrupts the coupling between gene expression and the cell cycle, thereby preferentially sensitizing cancer or tumor cells to killing by a cytotoxic agent. In addition, release from the G1 block induced by inhibition of CDK4 and CDK6 can also lead to synchronous S phase entry, thereby enhancing the killing of replicating cancer cells by a cytotoxic agent. With timely inhibition of Cdk4/Cdk6, and synergistic killing of tumor cells, this combination therapy could substantially lower the doses of cytotoxic agents, therefore reducing treatment side effects. This combination therapy appears to be an effective, treatment for blood cancers with uncontrolled cell division, such as multiple myeloma, lymphoma and leukemia.

The combination of the ckd4/6 inhibitor, PD0332991 and the proteasome inhibitor, bortezomib, demonstrated synergistic tumor suppression in NOD/SCID mice injected with Luc+GFP+M1.S cells, a

treatment that typically causes the development of aggressive tumors. Serial noninvasive bioluminescence imaging was used to visualize the tumor mass. V, ventral; D, dorsal

Institution

Cornell University

Inventors

Maurizio DiLiberto
Xiangao Huang
Selina Chen-Kiang