Chasing Two Oncoproteins Across Dozens of Human Cancers

Blood and skin cancers are more sensitive to inhibiting the CDK6 protein. Breast, lung, colorectal and other cancers are linked to CDK4.

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The proteins CDK4 and CDK6 are well-known regulators of the cell cycle, driving cells into the DNA replication phase that occurs before cell division. Since their discovery in the 1990s, scientists have understood that mutations in these regulatory proteins can lead to uncontrolled cell division, or cancer. Thanks to persistent research efforts over the past thirty years, CDK4/6 inhibitors have been approved for the treatment of breast cancer, but given the disruptive power of these oncoproteins, it is likely that such inhibitors could be effective for other types of cancer as well. When it comes to targeted therapies, more specific means less toxic, so understanding which proteins to target in each cancer is a crucial first step.

At Dana-Farber Cancer Institute, pioneer of cancer genomics and former Damon Runyon Fellow Matthew Meyerson, MD, PhD, is laying the groundwork for future studies to match cancer patients with the right CDK inhibitor. Recently, his lab analyzed data from The Cancer Genome Atlas (an initiative Dr. Meyerson himself piloted from 2006 to 2018 that compiled and characterized data from hundreds of thousands of patient samples for open-source use in research) alongside CRISPR-induced gene deletions to measure the effects of CDK4 and CDK6 loss in dozens of human cancers. Their comprehensive investigation sheds light on the untapped potential of CDK4/6 inhibition.

Overall, the team found that adenocarcinomas—that is, cancers of mucus-producing glandular cells, such as breast, lung, esophageal, stomach, colorectal, pancreatic, prostate, and uterine cancers—are more dependent on CDK4 mutants, and therefore more sensitive to CDK4 inhibition. Blood cancers and skin cancers, on the other hand, are more sensitive to CDK6 inhibition.

The researchers also found a subset of cancer cells that were not dependent on either CDK4 or CDK6, but on another CDK protein, known as CDK2. This suggests an alternative pathway to target in order to stop uncontrolled cell proliferation.

Together, these findings describe the landscape of CDK4 and CDK6 dependency across human cancers, pinpointing specific cancer cell populations that might respond best to targeted therapy. With further research into these promising scenarios, more patients may benefit from CDK4 and

CDK6 inhibitors, bringing the work of three decades closer to fruition.

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