Research illuminates a therapeutic strategy to induce cancer cell death

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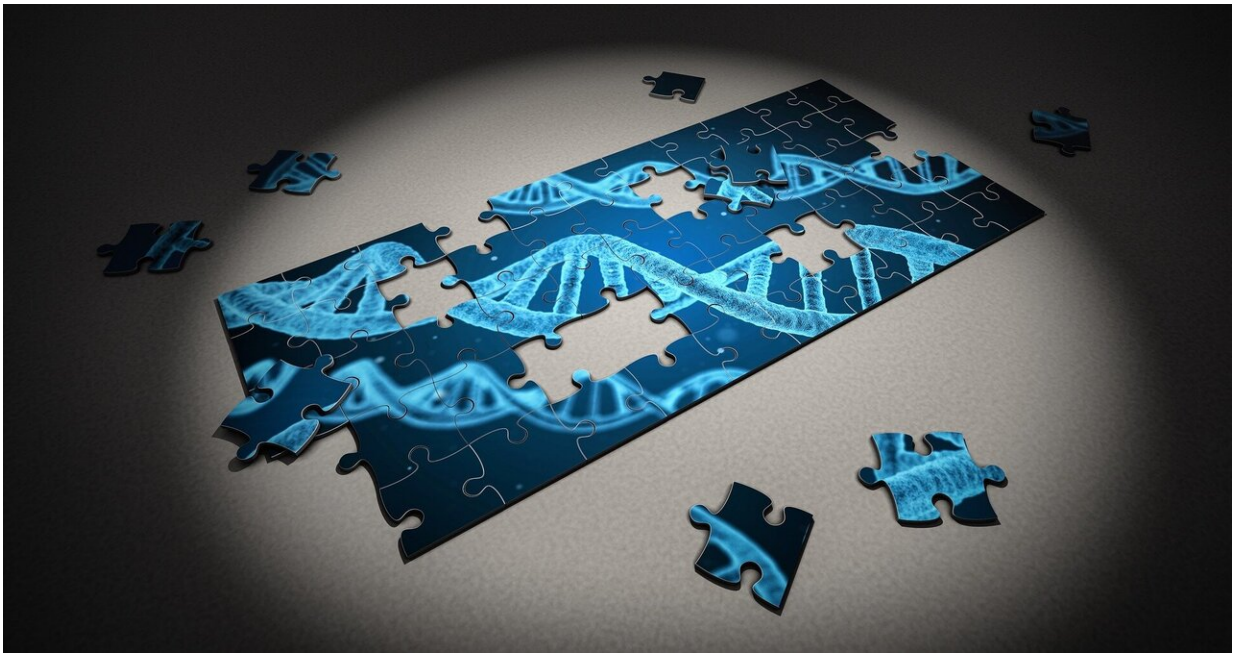

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Cancer is a disease driven by gene mutations. These mutated genes in cancer fall into two major categories: tumor suppressors and oncogenes. Mutations in tumor suppressor genes can allow tumors to grow unchecked—a case of no brakes—while mutations in oncogenes can activate cell proliferation, pushing the gas pedal all the way to the floor.

Researchers studying mutations in tumor suppressor genes have dedicated significant focus to p53, the most frequently mutated tumor suppressor gene in human cancers. Over the past two decades, much effort has been devoted to designing biologically targeted therapies that specifically activate p53.

However, while research has shown that these therapies are effective at inducing p53 activity, they generally can't kill cancer cells. As observed for other biologically targeted therapies, activation of p53 has been shown to stop tumor growth for a period of time, but the cells eventually mutate and become resistant to treatment.

New research by University of Colorado Cancer Center scientists illuminates the mechanisms at work that prevent p53 activation from triggering effective cancer cell death. They show that inhibiting two distinct repressors of p53 can elicit cancer cell death through activation of a complementary gene network known as the Integrated Stress Response.

"When you block both the major p53 repressor, known as MDM2, and its minor repressor, known as PPM1D, p53 works much better in terms of inducing cancer cell death, and this enhanced killing activity requires the Integrated Stress Response" explains Joaquin Espinosa, Ph.D., a professor of pharmacology in the CU School of Medicine, director of the Linda Crnic Institute for Down syndrome, and senior author of the study. "This is an important step in making p53-based biologically targeted therapies more effective."

Inducing cancer cell death

This development is an important milestone in almost two decades of research conducted by Zdenek Andrysik, Ph.D., an assistant research professor of pharmacology in the CU School of Medicine, and other

members of the Espinosa lab. Their and other research has worked to understand the role of MDM2 and PPM1D, two proteins that repress p53 inside tumor cells, and the mechanisms by which inhibiting them leads to cancer cell death.

"It was already established that MDM2 is a major repressor and PPM1D is a minor one," Espinosa explains. "For a long time, the hope was that inhibiting just the major repressor would suffice. Much effort was invested in developing small molecules that block MDM2, millions of dollars were spent, but these drugs performed poorly in clinical trials."

Researchers then turned to minor repressors, including PPM1D. "A lot less is known about PPM1D and other minor repressors of p53," Andrysik says, "but it soon became clear that if you inhibit both MDM2 and PPM1D, p53 can effectively induce cancer cell death. However, the underlying mechanisms driving this synergy were unknown".

Understanding the mechanisms

Espinosa and Andrysik have been able to demonstrate that inhibiting MDM2 and PPM1D activates the Integrated Stress Response, which is a signaling pathway that stimulates a protein called ATF4. They further demonstrated that ATF4 partners with p53, working together to cause cancer cell death.

Inhibiting MDM2 and PPM1D, and thus allowing p53 to partner with ATF4 in taking cancer cells to death, has shown promise for multiple cancer types in the laboratory, Andrysik says. This mechanistic insight quickly revealed additional pharmacological strategies to induce cancer cell death.

For example, Andrysik and Espinosa repurposed the drug Nelfinavir, which originally was approved as an HIV therapy. "Now we know that

Nelfinavir activates the Integrated Stress Response, thus becoming a great combination with MDM2 inhibitors," Espinosa says.

Andrysik and Espinosa are continuing their research to understand more about mechanisms of the synergistic response that happens when MDM2 and PPM1D are inhibited and p53 is activated. "Our data indicates that cancer cells are particularly vulnerable to this dual activation of p53 and the Integrated Stress Response, which may offer a therapeutic window in the clinic, sparing normal cells from the killing effects of p53," Andrysik says.

Espinosa adds that "a holy grail of cancer research has been the restoration of p53 activity to induce tumor regression. For the past 20, 30 years, a lot of research efforts have been devoted to finding more elegant solutions to broadly acting chemotherapy or radiation. As we learn more about the genes and proteins mutated in cancer, we're more able to see when the brakes are failing and restore them, or when the gas pedal is all the way to the floor and lift it with specifically targeted inhibitors."

More information: Zdenek Andrysik et al, PPM1D suppresses p53-dependent transactivation and cell death by inhibiting the Integrated Stress Response, *Nature Communications* (2022). DOI: 10.1038/s41467-022-35089-5

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