Finding the weak points of cancer cells

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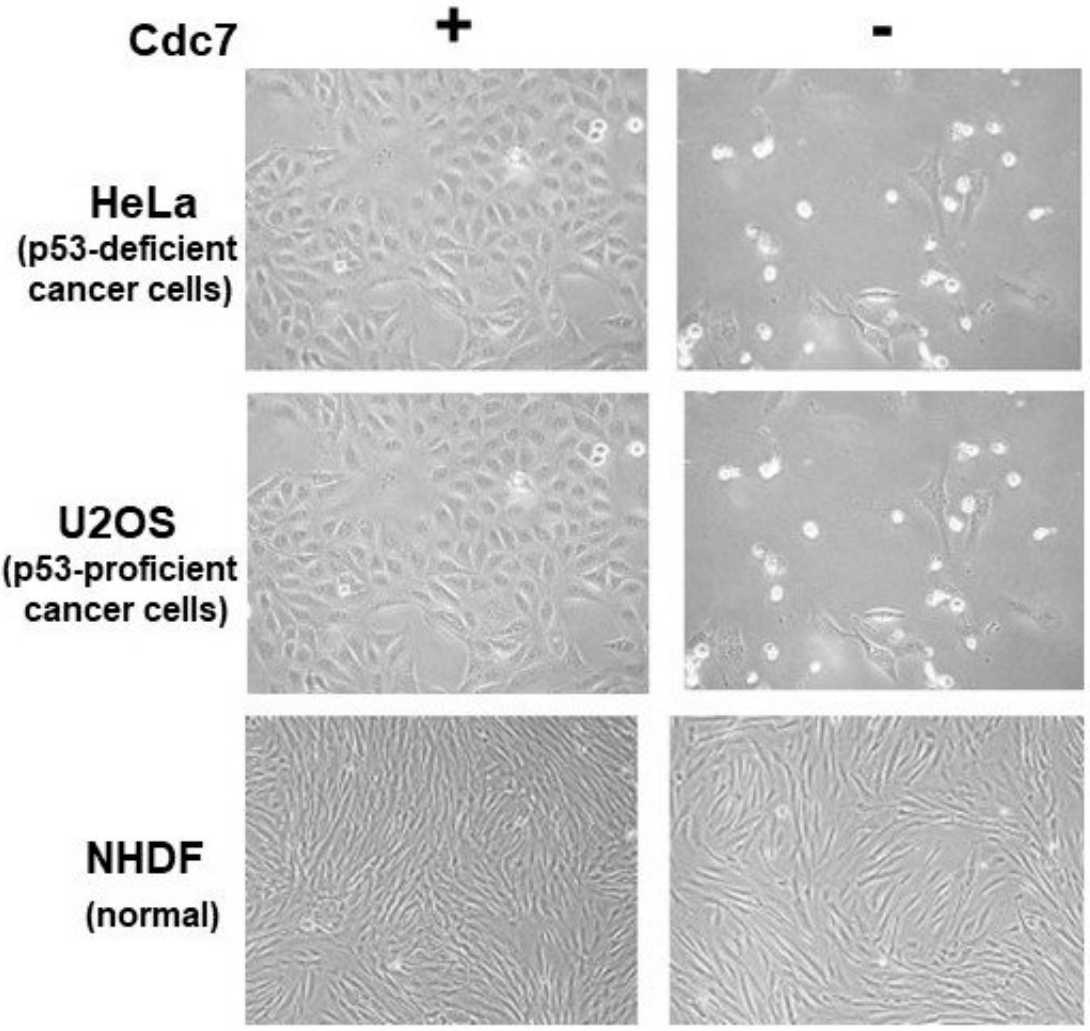

In both p53-defiencient and -positive cancer cells (HeLa [Human Cervix Epitheloid Carcinoma] and U2OS [Human Osteosarcoma], respectively), Cdc7 depletion results in cell death, whereas the same treatment does not affect the growth of non-cancer cells (NHFD; Normal Human Dermal Fibroblast) Credit: Tokyo Metropolitan Institute of Medical Science

The key to effective cures for cancers is to find weak points of cancer cells that are not found in non-cancer cells. Researchers at the Tokyo Metropolitan Institute of Medical Science found that cancerous and non-cancerous cells depend on different factors for survival when their DNA replication is blocked. Drugs that inhibited the survival factor required by cancer cells would selectively make cancer cells more vulnerable to replication inhibition.

DNA replication, copying the 3 billion base pairs of the human genome, takes six to eight hours. During this time, cells can encounter many problems that interfere with the copying process. DNA consists of long chains of nucleotide bases, and obstacles such as DNA interacting compounds, damaged bases, cross-linked DNA strands, reductions in nucleotide precursors, blockage by DNA binding proteins, unusual secondary structures of template DNAs, and collision with transcription can all contribute to blocking replication. It is essential for growing cells to overcome these problems to ensure that the entire genome is copied accurately. If cells cannot cope with these crises, the genome is likely to undergo changes that could cause cancer cells to develop.

Cells have evolved elaborate mechanisms to protect against damage from faulty DNA replication. When DNA replication machinery encounters an obstacle preventing replication, it activates a safety mechanism known as replication checkpoint. Replication checkpoint stops DNA replication and activates repair pathways. A critical protein in this process is called Claspin. When replication is blocked, a phosphate is covalently attached to Claspin in a process known as phosphorylation. Phosphorylation of Claspin is a critical first step in activating the replication checkpoint.

Recently, Chi-Chun Yang and his colleagues at the Tokyo Metropolitan

Institute of Medical Science determined how Claspin is phosphorylated. Their findings were reported in the 2019 December issue of *eLife*. By using genetically modified animals and cells as well as biochemical analyses with purified proteins, they found that when DNA replication is blocked in cancer cells, a protein called Cdc7 predominantly phosphorylates Claspin to activate the replication checkpoint. In contrast, in non-cancer cells, a different protein, CK1γ1, phosphorylates Claspin when DNA replication is blocked. The reason for this difference is because cancer cells have high amounts of Cdc7, while non-cancerous cells have low amounts of Cdc7 and relatively high amounts of CK1γ1. The results show an example of differential cellular strategies to deal with crisis between cancer and non-cancer cells.

Cancer cells are generally more sensitive to replication block than non-cancer cells, since cellular protection mechanisms are often compromised in cancers. Understanding how cells respond to cellular crises such as DNA replication block is crucial to developing new strategies for cancer treatments. Hisao Masai, Ph.D., the senior author of the *eLife* article, says, "We can take advantage of the different mechanisms utilized by cancer and non-cancer cells to devise a way to specifically target cancer cells. Our findings suggest that inhibiting Cdc7 will efficiently inactivate the safe-guard system against replication block selectively in cancer cells, leading to their clearance by cell death. Indeed, we and others have developed low molecular-weight compounds that specifically inhibit Cdc7 as candidate anti-cancer agents."

More information: Chi-Chun Yang et al, Cdc7 activates replication checkpoint by phosphorylating the Chk1-binding domain of Claspin in human cells, *eLife* (2019). DOI: 10.7554/eLife.50796

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