One protein, two important roles

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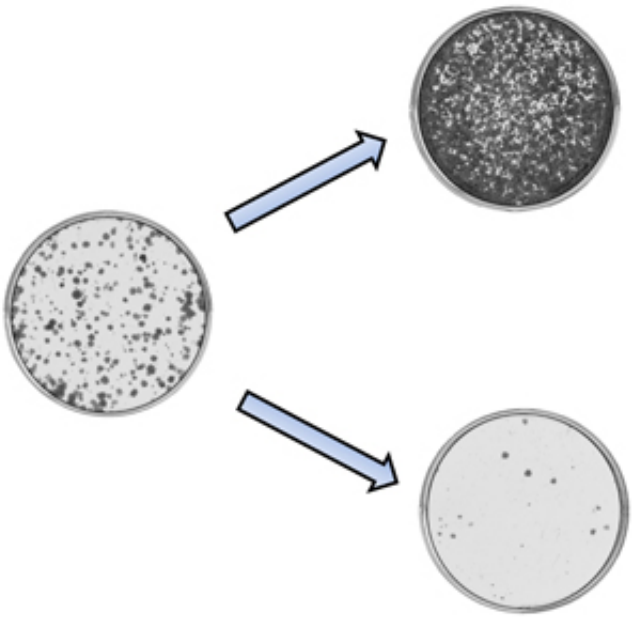

The effect of E2F-1 methylation patterns on cancer cell growth: symmetric methylation of E2F-1 promotes growth of cancer cells (top right), while asymmetric methylation of E2F-1 promotes apoptosis and death of cancer cells (bottom right). Credit: A*STAR Genome Institute of Singapore

The molecular pathways involved in the cell cycle are complex and difficult to control. Better understanding of cell control mechanisms, and why they go wrong in cancer, could help open the door to more effective cancer drug therapies.

Now, Shunsheng Zheng from the A*STAR Genome Institute of Singapore, together with an international research team, has revealed the

details of one intricate control mechanism. Their study focused on a protein called E2F-1, which is critical in the cell cycle for its role in regulating the expression of many genes involved in cell growth and replication.

"Inhibition of E2F-1 and its close cousins, E2F-2 and E2F-3, completely prevents cells from growing, so we are reasonably certain that E2F activity plays a key role in promoting cell growth," explains Zheng. "But a series of studies have shown that hyper-activation of E2F-1 can trigger a form of cellular suicide known as apoptosis."

As E2F-1 has been shown to both enhance and reduce cell growth under different conditions, Zheng and his colleagues set out to determine the molecular mechanisms that underlie these opposing roles.

As with most proteins, molecular tags are added to specific sites on E2F-1 in a process called methylation. The researchers discovered that, in a particular region of E2F-1, methylation can occur in one of two ways: symmetric (SDMA) or asymmetric (ADMA). They showed that these two states are the key to understanding the opposing roles of E2F-1.

"We removed SDMA from E2F-1, which resulted in an increase in apoptosis and a decrease in cell growth," says Zheng. "When we removed ADMA from E2F-1, the effect was opposite; we observed an increase in cell growth and replication."

Furthermore, the team found that DNA damage in cells usually enhances the type of E2F-1 methylation that promotes apoptosis and thereby protects against cancer. But in cancerous cells this mechanism does not work, meaning that the team's findings could help to improve existing cancer therapies.

"Some of the most common anti-cancer drugs, such as doxorubicin, work by re-activating the DNA damage response machinery," explains Zheng. "Doxorubicin is able to remove SDMA from E2F-1 and trigger apoptosis in cancer cells, but in a molecular sense it works like a shotgun. The pellets fly everywhere, resulting in adverse effects such as heart problems, nausea, vomiting and hair loss. So, by carefully mapping out the way in which our cancer target molecules work, we hope to create an anti-cancer drug that works more delicately."

More information: Zheng, S., Moehlenbrink, J., Lu, Y-C., Zalmas, L-P., Sagum, C.A. et al. Arginine methylation-dependent reader-writer interplay governs growth control by E2F-1. *Molecular Cell* 52, 37–51. (2013). dx.doi.org/10.1016/j.molcel.2013.08.039

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