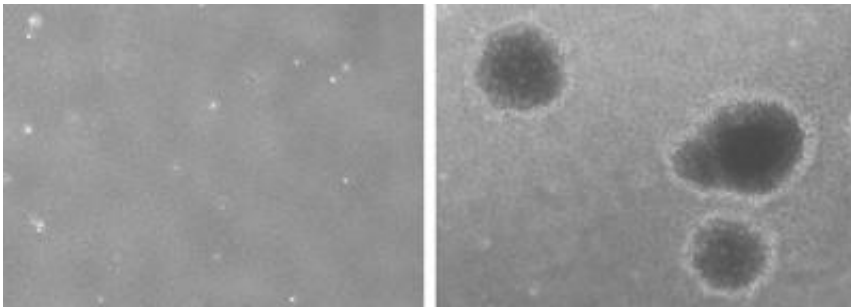


Mdm2 suppresses tumors by pulling the plug on glycolysis

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Mouse cells fail to thrive in suspension cultures when wild-type Mdm2 is expressed (left), but expression of a mutant form of Mdm2 (right), in combination with PGAM and an oncogenic protein called Ras, enhances glycolysis and promotes cell transformation (right). Credit: Mikawa et al., 2014

Cancer cells have long been known to have higher rates of the energy-generating metabolic pathway known as glycolysis. This enhanced glycolysis, a phenomenon known as the Warburg effect, is thought to allow cancer cells to survive the oxygen-deficient conditions they experience in the center of solid tumors. A study in *The Journal of Cell Biology* reveals how damaged cells normally switch off glycolysis as they shut down and shows that defects in this process may contribute to the early stages of tumor development.

Various stresses can cause cells to cease proliferating and enter an inactive state known as "senescence" that prevents their transformation

into [tumor cells](#). In 2005, Hiroshi Kondoh and colleagues found that cells normally limit [glycolysis](#) as they enter senescence and that increasing the levels of the glycolytic enzyme PGAM can prevent cells from exiting the cell cycle. PGAM is increased in many tumors, stimulating glycolysis and other important pathways. But how cells regulate PGAM has been unclear.

Working at Kyoto University in Japan, Kondoh and colleagues followed up on their previous work and found that, in response to DNA damage or oncogene expression, PGAM was degraded, thereby inhibiting glycolysis as the [cells](#) entered senescence. The enzyme Mdm2 targeted PGAM for degradation in response to these senescence-inducing stresses.

"Mdm2 can clearly, in some cases, act as a tumor suppressor by destabilizing PGAM," says Kondoh. Recent studies have emphasized the importance of PGAM as a therapeutic target for cancer management. Identifying the modulators of PGAM stability might open up new avenues for intervention.

More information: ikawa, T., et al. 2014. *J. Cell Biol.* [DOI: 10.1083/jcb.201306149](#).

Kondoh, H., et al. 2005. *Cancer Res.* 65:177-185.

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