Molecular switch identified that controls key cellular process

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The body has a built-in system known as autophagy, or 'self-eating,' that controls how cells live or die. Deregulation of autophagy is linked to the development of human diseases, including neural degeneration and cancer.

In a study published online this week in the Proceedings of the National Academy of Sciences, scientists at the Ludwig Institute for Cancer Research in Oxford discovered a critical molecular switch that regulates autophagy. They also studied the links between autophagy and a cellular process called senescence that stops cell growth permanently.

The researchers identified ASPP2, a tumor suppressor, as a molecular switch that can dictate the ability of a common cancer gene, known as the RAS oncogene, to either stop or promote senescence.

As Yihua Wang and researchers in Xin Lu's group at the Ludwig Institute investigated the life cycle of fibroblast cells – the most common connective tissue cells in animals – they found that reduced levels of the ASPP2 protein increase RAS oncogene-induced autophagic activity. This in turn prevented cells from entering senescence. Without ASPP2, the cells continued to proliferate unchecked, thereby promoting tumor growth.

ASPP2 is known to play a role in suppressing tumor development. Mice that have a deficiency or malfunction in this protein have a predisposition to developing tumors. And low ASPP2 levels in patients

are linked to poor prognoses in cancers, such as large B-cell lymphomas. Reduced ASPP2 expression has also been observed in highly metastatic breast tumors. But until now, researchers did not understand why.

"We found that in the presence of the common cancer-causing RAS oncogene, ASPP2 interacted with a protein complex that is responsible for deciding cell fate via autophagy," said Yihua Wang, PhD, Ludwig researcher in Oxford.

"What this means is that the cell's emergency stop button is disabled when ASPP2 expression is reduced or lost, allowing it to proliferate unchecked as with cancer," added Wang.

"The balance between the RAS oncogene and ASPP2 activity is crucial to determining whether or not tumor growth is promoted. Our next step will be to identify ways to alter ASPP2 activity at that critical switch point. This could be an effective way to treat cancers with reduced ASPP2 expression and mutated RAS, such as breast and colon cancers," concluded Wang.

"Some of the recently developed anti-cancer drugs are potent inducers of autophagy. The new findings may also offer an explanation as to why patient response to these drugs can vary dramatically. There are factors at play within the body that can dictate authophagic activity and impact clinical outcomes," said Xin Lu, PhD, director of Ludwig's Oxford Branch. "While further study is needed, these findings may in the longer term help doctors to identify patients who are more likely to respond well to autophagic inhibition," added Lu.

Provided by Ludwig Institute for Cancer Research