Bacterial peptide provides new insight into common tumor suppressor

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Scientists have identified a new antitumor drug that might prove useful in developing treatments for a multiple human cancers. The research, published by Cell Press in the July 8 issue of the journal *Cancer Cell*, advances the understanding of one of the most frequently disrupted tumor suppressor proteins in human cancer and provides new insight into the regulation of the complex process of cellular protein degradation under normal and pathological conditions.

"The cyclin kinase inhibitor p27kip1 is one of the most frequently dysregulated tumor suppressor proteins in human cancers and it correlates directly with patient prognosis," explains study author Dr. Nisar P. Malek from Hannover Medical School in Germany. "Due to increased turnover, p27kip1 is not sufficiently expressed in many human cancers. Therefore, targeting the p27kip1 degradation machinery might prove beneficial in the treatment of a variety of human malignancies."

Dr. Malek and colleagues had previously shown that stabilization of p27kip1 reduced progression of intestinal cancer. They sought to build on this earlier work by seeking to identify substances that reduce or block p27kip1 turnover and thereby allowing re-expression of the protein in tumor tissues. Using a cell screening assay, the researchers identified the peptide argyrin A, derived from the myxobacterium Archangium gephyra, as a stabilizer of p27kip1 and a potent, broadly acting antitumor drug.

Argyrin A induced apoptosis in cancer cells, prevented new tumor blood

vessels from forming and targeted existing tumor blood vessels. Importantly, all antitumor activities of argyrin A depended on expression of p27kip1 and resistance to argyrin A was directly linked to loss of p27kip1. The researchers went on to reveal that the mechanism by which argyrin A reduces turnover of p27kip1 involves inhibition of the 20S proteasome, a complex that is involved in destruction of the majority of cellular proteins.

These findings show that argyrin A is a proteasome inhibitor that prevents turnover of p27kip1 and exerts potent antitumor activities. "The unique properties of argyrin A combined with its high activity at well-tolerated levels make this compound a good candidate for further clinical development," concludes Dr. Malek.

Source: Cell Press