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Viral mimic induces melanoma cells to digest themselves

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Recent research has uncovered an unexpected vulnerability in deadly melanoma cells that, when exploited, can cause the cancer cells to turn against themselves. The study, published by Cell Press in the August issue of the journal *Cancer Cell,* identifies a new target for development of future therapeutics aimed at selectively eliminating this aggressive skin cancer which is characterized by a notoriously high rate of metastasis and treatment-resistance.

"Although considerable effort has been devoted to the search for molecular mechanisms that contribute to the chemo- and immunoresistance of melanoma, the average survival of patients with inoperable metastases remains less than 10 months," explains senior study author Dr. Maria S. Soengas from the Melanoma Laboratory at the Spanish National Cancer Research Centre in Madrid, Spain. Melanoma has multiple complex genetic aberrations that make the cells difficult to destroy with current treatments.

One process that has not been studied in great detail with regards to melanoma is a type of autophagy (literally, self-eating) that involves sequestration of components within the cell for eventual degradation. Previous work has linked autophagy with both cancer cell death and survival and it is not clear whether this process might be a viable target for future drug development. Dr. Soengas and colleagues designed a series of studies to examine the interplay between autophagy and cell death in the context of tumor cell-selective elimination of melanoma cells.

The researchers discovered that melanoma cells retain the ability to recognize and respond to double-stranded RNA (dsRNA) located inside the cell cytoplasm. Most animal cells contain single-stranded RNA and see dsRNA, which is associated with viruses, as a threat. The melanoma cells responded to administration of the dsRNA mimic polyinosine-polycytidylic acid (pIC) by inducing an immune response that led to autophagy. However, the method of delivering the pIC to the melanoma cells was critical and required a carrier called polyethyleneimine (PEI) to ensure delivery of pIC to the cell cytoplasm.

The researchers went on to show that pIC links autophagy to apoptosis, a well studied cell death pathway. Significantly, the cell autonomous anti-tumor activity of pIC was observed even in animals with a suppressed immune system, a condition common to melanoma patients. "Altogether, our results provide the proof of principle for dsRNA sensors as therapeutic targets to overcome the inherent resistance of melanoma cells to current anticancer treatments," says Dr. Soengas.

Importantly, the pIC-PEI complex has two exciting advantages over other anticancer agents. "First, pIC-PEI can induce both autophagy and apoptosis in an efficient manner while other compounds are just partial inducers of one of the two processes. Second, pIC-PEI has a significant anti-melanoma activity in experimental mouse models without noticeable side effects." The researchers caution that further research is required before these results can be translated to the clinic.

Source: Cell Press (news : web)