Contents

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PERSPECTIVES

COMMENTARY

MINIREVIEW

RESEARCH ARTICLES

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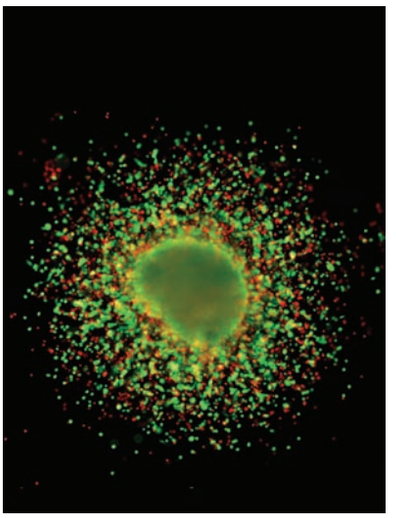
ABOUT THE COVER



Autophagy is a critical factor in cancer and in the development and progression of diseases associated with increased cancer risk. As a cytoprotective survival pathway, autophagy prevents chronic tissue damage that can lead to cancer initiation and progression; stimulating or restoring autophagy may prevent cancer. Once cancer occurs, however, autophagy can enhance cancer-cell fitness and survival. Moreover, many cancer therapeutics stimulate autophagy that may be a resistance mechanism. These findings suggest the possible benefit of autophagy inhibition in established cancers. The cover features a fluorescence image (courtesy of Drs. Xiaoqi Xie and Eileen White) of a representative melanoma (UACC903) spheroid (a colony of cells growing in three dimensions *in vitro* and simulating tumor growth) after treatment with the mammalian target of rapamycin (mTOR) inhibitor and autophagy stimulator CCI-779 (temsirolimus) and with the autophagy inhibitor hydroxychloroquine. UACC903 cells were added to plates coated with 1.5% agar and incubated in growth medium until spheroids had formed (after 72 hours). The spheroids were then harvested and implanted into a gel of collagen type-I matrix, to which growth medium with the test drugs was added on top. After 72 hours, cell death was imaged by a two-color fluorescence cell-viability assay, with green representing live and red representing dead cells. Cell death is not apparent with either agent alone, whereas the combination of an autophagy and mTOR inhibitor induces cell death (as shown) and reduces spheroid size. See article by Chen and White (beginning on page 973) for more information on the emerging understanding of the importance of autophagy to cancer prevention.

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4 (7)

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