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Autophagy suppresses melanoma tumorigenesis by inducing senescence

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Whether and how autophagy is involved in tumorigenesis is poorly understood. We approached this question by investigating a relatively large cohort of patients with mostly early primary melanoma for their expression of 2 markers for autophagy, the protein ATG5 (autophagy-related 5) and MAP1LC3B/LC3 (microtubule-associated protein 1 light chain 3B). Surprisingly, we discovered that both ATG5 and LC3 levels are decreased in patients with melanomas as compared with those with benign nevi. We wondered why reduced autophagy should facilitate early tumor development. Using an in vitro model of melanoma tumorigenesis, in which a mutated oncogene, BRAF (v-raf murine sarcoma viral oncogene homolog B), had been introduced into normal human melanocytes, we were able to show that downregulation of ATG5 promoted the proliferation of melanocytes because it facilitated bypassing oncogene-induced senescence (OIS). Our work supports previous reports that had argued that autophagy actually suppresses tumorigenesis and explains the possible mechanism. Furthermore, our findings suggest that the status of ATG5 and autophagy could serve as a diagnostic marker for distinguishing benign from malignant tumors of melanocytes.

Compared with the large amount of autophagy-related data accumulated with cancer cells receiving anticancer drug treatment, the role of autophagy in tumorigenesis has been little investigated and is poorly understood. Using immunohistochemistry to assay for ATG5 expression in 194 primary melanomas and 150 benign nevi, we found that the level of ATG5 is diminished in primary melanoma as compared with nevi cells. In contrast to ATG5, the expression of BECN1 is indistinguishable in melanomas and nevi. Moreover, we observed in melanomas as compared with nevi strikingly low levels of LC3 and high levels of SQSTM1/p62, 2 marker proteins that are indicators for the status of autophagy, thus documenting a reduced basal level of autophagy in vivo. Reduced autophagy is associated with a lowered progression-free survival of these patients as evidenced by a follow-up on 158 primary melanoma patients: patients exhibiting higher levels of ATG5 in their tumor cells experience better progression-free survival than those with lower levels.

Having failed to find deletion or point mutations within the ATG5 gene, we examined epigenetic alterations to discover a mechanism for downregulation of ATG5 in melanoma. Using DNA extracted from paraffin-embedded tumors, we found that the promoter of ATG5 is methylated in 9 of 13 randomly selected primary melanomas, but in only 1 of 15 nevi. The expression of ATG5 could be restored by treatment of melanoma cells exhibiting ATG5 promoter methylation with the DNA methyltransferase inhibitor 5-aza-2’-deoxycytidine in cell culture. These data indicate that promoter methylation is at least one of the mechanisms leading to the downregulation of ATG5. Epigenetic modifications of ATG5, including promoter methylation, should be further investigated on a larger scale in order...
to better understand the mechanisms responsible for diminished expression of ATG5 in melanoma.

On the one hand, reduced ATG5 expression directly affects basal levels of autophagy and the ability of melanoma cells to respond to autophagy inducers. Overexpression of ATG5 in melanoma cells, on the other hand, increases the basal and the induced levels of autophagy. Furthermore, overexpression of ATG5 inhibits melanoma cell proliferation when the colony-forming abilities of these cells is examined. Interestingly, the majority of these ATG5-overexpressing melanoma cells are also positive for senescence-associated β-galactosidase. Senescence, a cellular aging process, occurs not only in cultured cells in vitro, but also in vivo. As a failsafe mechanism to avoid carcinogenesis, senescence has also been described in several benign tumors, of which the melanocytic nevus is the best described. Using an in vitro model in which BRAFV600E is overexpressed in primary melanocytes, in order to investigate melanoma tumorigenesis, we were able to show that lowering ATG5 expression leads to a reduced basal level of autophagy accompanied by increased cell proliferation and an interdiction of OIS in melanocytes. These data, although generated in vitro, suggest a mechanism by which benign tumor cells may fail to enter OIS, thereby transforming into malignant cells owing to a deficit in autophagy (Fig. 1).

Taken together, our data indicate that ATG5 and autophagy may be actively involved in the tumorigenesis of melanoma by promoting senescence. Furthermore, these findings raise serious questions about the use of autophagy inhibitors as a general approach in fighting cancer. Future studies will be required to evaluate the expression of other ATGs in melanoma and in other types of cancer to obtain a general picture about the role of autophagy in tumorigenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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