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Scientists discover a specific molecular biomarker for malignant melanoma

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Melanoma is one of the types of cancer that poses the greatest challenge to researchers because it manifests in many ways, it contains a large number of mutations and displays high metastatic capacity. To date, clinicians mostly base their diagnoses on observation, such as by measuring thickness—a tumour depth of only two millimetres implies a poor prognosis.

Now, however, in a study aimed at identifying oncogenes that are particularly altered in this tumour type, scientists from the Melanoma Group at the Spanish National Cancer Research Centre (CNIO), headed by Marisol Soengas, have discovered a peculiarity of melanomas that might make them vulnerable: Patients with partial loss of a protein called ATG5 have a worse prognosis, developing metastasis and resistance to drugs. The results of this study have been published today in the journal *Autophagy*.

The "key" that regulates the metastatic capacity of melanoma

The ATG5 protein is essential for autophagy; a process that is usually beneficial for cells to self-degrade their own components when they are no longer useful. However, autophagy can be a double-edged sword for tumour cells—any excess self-cannibalism can be harmful, so cells carefully regulate the process. However, the factors that act as "keys" or switches of autophagy are still unknown today.

"In this study, we wanted to discover to which extent autophagy is important for melanomas in comparison with other pathologies, and set to investigate mechanisms that underlie dual pro- and anti-tumourigenic functions of this process," says Marisol Soengas. "We analysed up to 20 autophagy genes in more than 25 types of cancer using databases that contained information of almost 5,000 patients. We proved a huge variability between the different types of tumours. However, we found alterations in the ATG5 gene that only provided diagnostic value in melanoma." In particular, they demonstrated that melanoma cells limit ATG5 levels in a very specific way, by selectively losing one of the copies of this gene, a process that does not occur in relation to other autophagy factors.

To study the role of ATG5 in vivo, they created genetically modified mice with induced selective loss of one of the copies of the ATG5 gene. The researchers found that when only one copy of this gene is lost, the tumours have a poor prognosis (metastasis and death) just as they had observed in patients.

Further, in these animal models, the team also made another observation of potential therapeutic value: "We discovered that when tumours lose only one copy of ATG5, they not only become more aggressive and metastatic, but also respond worse to current drugs used for targeted therapies in melanoma," explains the researcher.

"Therefore, we have a switch that regulates autophagy and favours metastasis. We believe that this information will greatly enhance our capacity to predict prognosis." In other words, doctors could use the genetic information on ATG5 to identify the risk of disease progression and to improve patient monitoring.

Implications for drug development

"This study has relevant implications for drug design, as it suggests that the partial blockage of autophagy could worsen the malignant behaviour of metastatic melanomas," says Soengas.

This molecular marker commonly found in cutaneous melanoma will also open up other areas of research on less common and less-studied melanomas, such as ocular or mucous melanomas. "The chromosome where ATG5 resides is lost in ocular melanoma, which suggests that it is worth exploring its role in this type of melanoma," concludes Soengas.

More information: María García-Fernández et al, Metastatic risk and resistance to BRAF inhibitors in melanoma defined by selective allelic loss of, *Autophagy* (2016). DOI: 10.1080/15548627.2016.1199301

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