Researchers selectively eliminate cells that express the oncogene RAS

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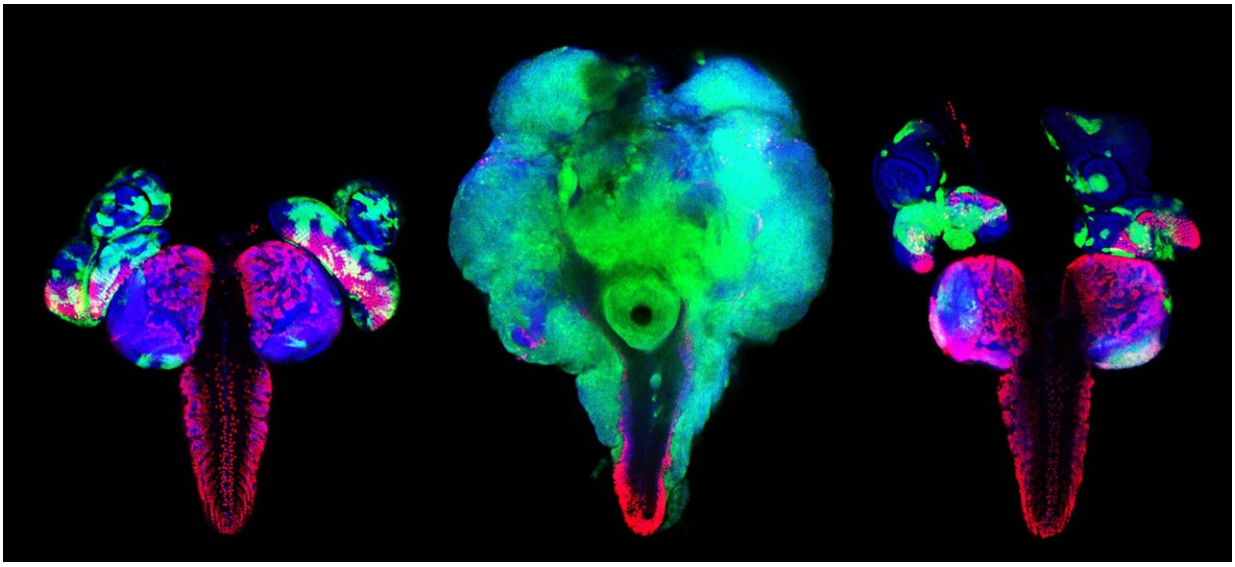

Proliferative and invasive capacity of tumour cells (centre) compared to normal cells (left) and effect of TRAMETINIB treatment, which reduces the invasive capacity and tumoural load (right). Credit: Marco Milán, IRB Barcelona

The RAS oncogene is activated in 30 percent of human cancers, and results in the proliferation and transformation of tumor cells. No effective inhibitor has been found for this protein to date.

ICREA researcher Marco Milán, head of the Development and Growth Control Laboratory at the Institute for Research in Biomedicine (IRB

Barcelona), has led a study published in *Cell Reports* that identifies the weak point of RAS-expressing cells.

Milán's lab used *Drosophila melanogaster* to demonstrate that the DNA damage caused by the high levels of cellular proliferation induced by RAS can be exploited therapeutically, thus paving the way to devising strategies to specifically eliminate tumor cells that activate it.

Milán says, "RAS-expressing cells duplicate their DNA very quickly. As a result, errors and DNA damage occur. We have shown that RAS blocks the repair of this damage. In normal cells, this would cause cell death through the activation of the p53 tumor suppressor protein. But RAS blocks the ability of this protein to cause cell death, and this is precisely the aspect that we have exploited with both gene therapy and chemistry."

In the study, the scientists used TRAMETINIB, a drug prescribed for human melanoma, to inhibit the ability of RAS to block cell death. This approach led to the elimination of malignant tumors selectively and by cell death, without affecting the development of organs or the flies themselves.

Lada Murcia and Marta Clemente, first authors of this study, write, "We have also shown that radiotherapy, which causes DNA damage, increases the sensitivity of RAS-expressing cells to gene therapy."

Milán says, "The results of the study open up the possibility of combining irradiation therapies with RAS inhibitors to selectively eliminate tumor cells."

More information: Lada Murcia et al. Selective Killing of RAS-Malignant Tissues by Exploiting Oncogene-Induced DNA Damage, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.06.004

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