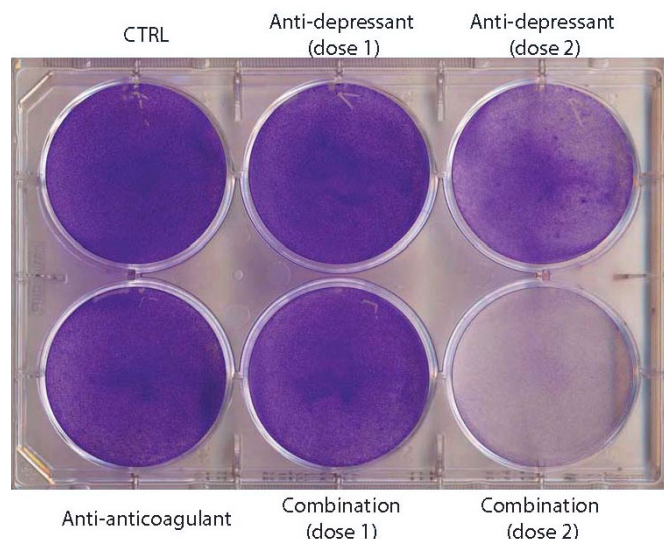


Antidepressants plus blood thinners cause brain cancer cells to eat themselves in mice

24 September 2015



Analysis of cell viability of equal numbers of human glioblastoma cells plated in a six-well cell culture dish, determined by crystal violet staining for live cells. The cells were treated for three days with a TCA (imipramine), the anti-coagulant (ticlopidine) or the combination of two, at two different concentrations. The purple color reflects millions of live cancer cells in a well, whereas the clearing and lack of purple stain is indicative of impaired proliferation and survival (cell death) of the glioblastoma cancer cells. Credit: Douglas Hanahan.

Scientists have been exploring the connection between tricyclic antidepressants and brain cancer since the early 2000s. There's some evidence that the drugs can lower one's risk for developing aggressive glioblastomas, but when given to patients after diagnosis in a small clinical trial, the antidepressants showed no effect as a treatment.

In a study appearing in *Cancer Cell* on September 24, Swiss researchers find that antidepressants work against brain cancer by excessively increasing tumor autophagy (a process that causes the *Cancer Cells* to eat themselves). The scientists

next combined the antidepressants with blood thinners—also known to increase autophagy—as a treatment for mice with the first stages of human [glioblastoma](#). Mouse lifespan doubled with the drug combination therapy, while either drug alone had no effect.

"It is exciting to envision that combining two relatively inexpensive and non-toxic classes of [generic drugs](#) holds promise to make a difference in the treatment of patients with lethal [brain cancer](#)," says senior study author Douglas Hanahan, of the Swiss Federal Institute of Technology (EPFL). "However, it is presently unclear whether patients might benefit from this treatment. This new mechanism-based strategy to therapeutically target glioblastoma is provocative, but at an early stage of evaluation, and will require considerable follow-up to assess its potential."

Mice received the combination therapy 5 days a week with 10-15 minute intervals between drugs. The antidepressant was given orally, and the other [drug](#) (the blood thinner or anti-coagulant) was injected. The data suggest that the drugs act synergistically by disrupting, in two different places, the biological pathway that controls the rate of autophagy—a cellular recycling system that at low levels enhances cell survival in stressful conditions. The two drugs work together to hyper-stimulate autophagy, causing the *Cancer Cells* to die.

"Importantly, the [combination therapy](#) did not cure the mice; rather, it delayed disease progression and modestly extended their lifespan," Hanahan says. "It seems likely that these drugs will need to be combined with other classes of anticancer drugs to have benefit in treating glioblastoma patients. One can also envision 'co-clinical trials' wherein experimental therapeutic trials in the mouse models of glioblastoma are linked to analogous small proof-of-concept trials in GBM patients. Such trials may not be far off."

More information: *Cancer Cell*, Shchors et al.:

"Dual targeting of the autophagic regulatory circuitry in gliomas with repurposed drugs elicits cell-lethal autophagy and therapeutic benefit"

[dx.doi.org/10.1016/j.ccell.2015.08.012](https://doi.org/10.1016/j.ccell.2015.08.012)

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