Myc inhibition is an effective therapeutic strategy against most aggressive brain tumors

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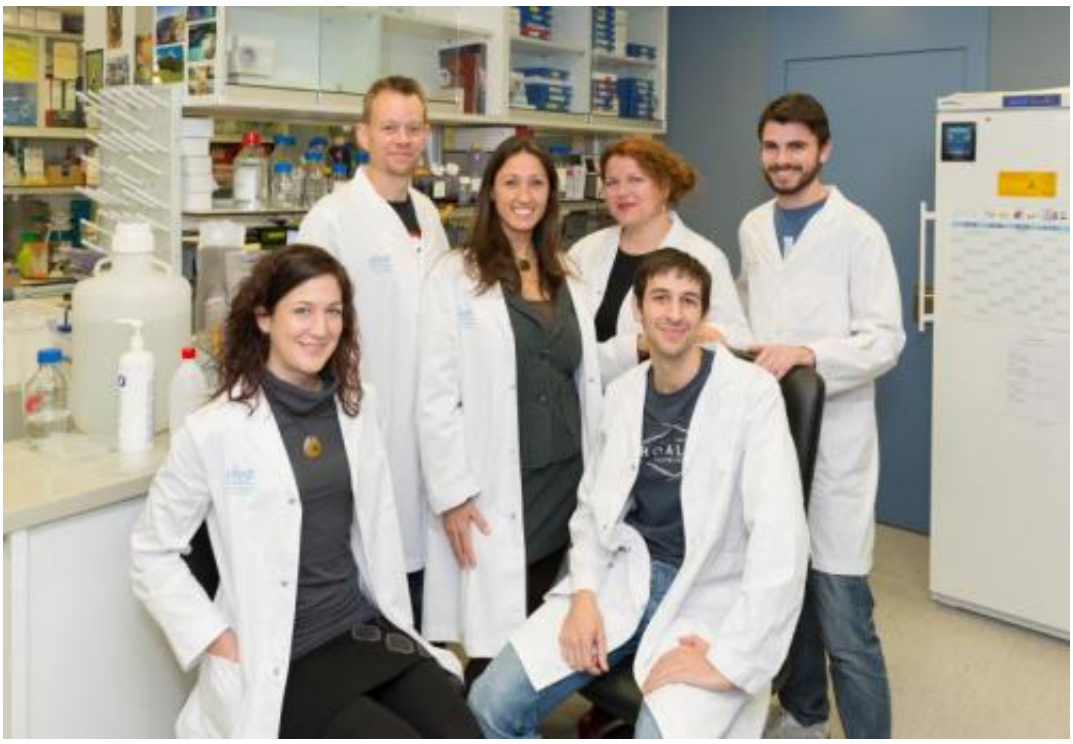

The "Mouse Models of Cancer Therapies" group. Credit: VHIO

Research led by the Vall d'Hebron Institute of Oncology (VHIO) evidence the most conclusive preclinical results to-date validating Myc inhibition as a therapeutic strategy in glioma – a highly agressive tumor type that notoriously outsmarts current anti-cancer therapies. The study

led by Laura Soucek, Principal Investigator of VHIO´s Mouse Models of Cancer Therapies Group, published today in *Nature Communications*, not only represents an important step forward in ultimately providing brain glioma patients with new therapeutic avenues, but also reveals new insights into the biology of Myc that could further impact on its therapeutic potential.

In a study published last year, the group succeded in eradicating lung tumors in transgenic mice by adopting the same strategy involving the expression of Omomyc, a Myc inhibitor designed by Soucek. They also confirmed that there were no side effects post-administration of repeated and long-term treatment. Importantly, there was no evidence of resistance to therapy—one of the greatest challenges in the treatment of cancer. These results therefore confirmed Myc inhibition as a sound and effective therapeutic strategy for the development of novel cancer drugs.

Soucek and her group were to raise the bar yet higher. Firstly, the focus on gene expression-based therapy under experimental study progressed and re-programed on the development of an administrable Omomyc-based drug. Second, the group continued to show the efficacy of Myc inhibition across different tumors and, above and beyond transgenic models, they showed the same success in human tumors using a technique that transfers human cancer cells to immunodeficient mice. "Upon reporting initial results at preclinical level, our main concern was how do demonstrate these findings in human tumors," says Laura Soucek. "Firstly, we focused on how they could apply to other tissues and other more aggressive tumor types for which there are no effective treatments, whereby an ´Omomyc solution´ could make all the difference. We also aimed to reveal new insights into the mechanism of action of Omomyc in tumor cells." It seems that Soucek's group has now found answers to all these questions. "All our efforts must now concentrate on finding a means for its pharmacological administration. Based on our research currently underway, we have every reason to be

optimistic" asserts Soucek.

A novel therapy for the most common and aggressive brain tumor

After four years´ exhaustive research, these latest results bring more good news and with them, preclinical Myc inhibition has also been validated as a therapeutic strategy against astrocytoma, a type of glioma, in vivo in mouse models and in vitro in stem cells of these tumors. In these models, which develop advanced brain tumors with clear neurological symptoms, treatment with the Omomyc transgene drastically reduces tumors and improves the associated symptoms until the mouse recovers and starts to act completely normally. Mice treated with Omomyc survived, whereas those without, did not. "We did not stop there," explains Soucek, "we applied therapy with Omomyc to both human glioblastoma cell lines and mice with patient-derived tumor xenografts that faithfully recapitulate human tumors." The therapeutic impact of Omomyc lies in its structure, which is similar to that of Myc, making it possible to block the transcription of genes controlled by this protein. Myc inhibition leads to "defects" in tumor cells and often results in their death by inducing mitotic aberrations, thus halting normal cell division.

"Our results undoubtedly show that Myc inhibition is effective in mouse tumors and, more notably, in human glioma." she explains. The group has demonstrated the additional therapeutic potential of Omomyc thanks to their clinically orientated approach aimed against the most common and aggressive primary tumor to affect the adult central nervous system – glioblastoma, for which there is a critical call to improve current therapies which are largely ineffective. "This is the very first time that the use of Omomyc in human tumor specimens have been validated. We have also confirmed that Myc inhibition is effective against the tumor

once it has developed, acts against tumor initiating cells, and prevents them from dividing, proliferating and forming the tumor again." continues Dr. Soucek.

Mitotic catastrophe as the therapeutic mechanism of Myc inhibition

The Myc protein plays an important role in regulating gene transcription, controlling the expression of up to 15% of human genes. It is also implicated in cellular proliferation, differentiation and apoptosis (programmed cell death which is necessary for tissue regeneration and the elimination of damaged cells). However, alterations in this protein trigger uncontrolled cell proliferation, which can result in cancers developing in different tissues. Myc deregulation is actually found in most tumors including cancer of the cervix, breast, colon, lung, pancreas, and stomach.

Brain tumors can now be added to this list of potential tumors that can be targeted with Myc inhibition.

At the cellular level, we now know more about its mechanism of action. Regardless of the experimental system used, Myc inhibition reduces proliferation and increases cell death. "Importantly, the cells we treated with Omomyc went crazy. They showed problems with cell proliferation, with aberrant mitosis and the formation of cells with many nuclei that then died through mitotic catastrophe, that is, due to the inability to divide properly" explains Laura Soucek. "If we do not allow Myc to function normally, tumor cells cannot divide efficiently." she affirms. Myc is not deregulated in healthy cells, hence, its inhibition does not generate any significant side effects that might limit the use of this therapy.

To conclude, Myc inhibition as a therapeutic strategy against brain tumors opens up new avenues signposting fresh hope and improved, more effective therapies for patients. Soucek and her team are consequently concentrating on translating their findings to the clinic. Preliminary results show promise.

Provided by Vall d´Hebron Institute of Oncology