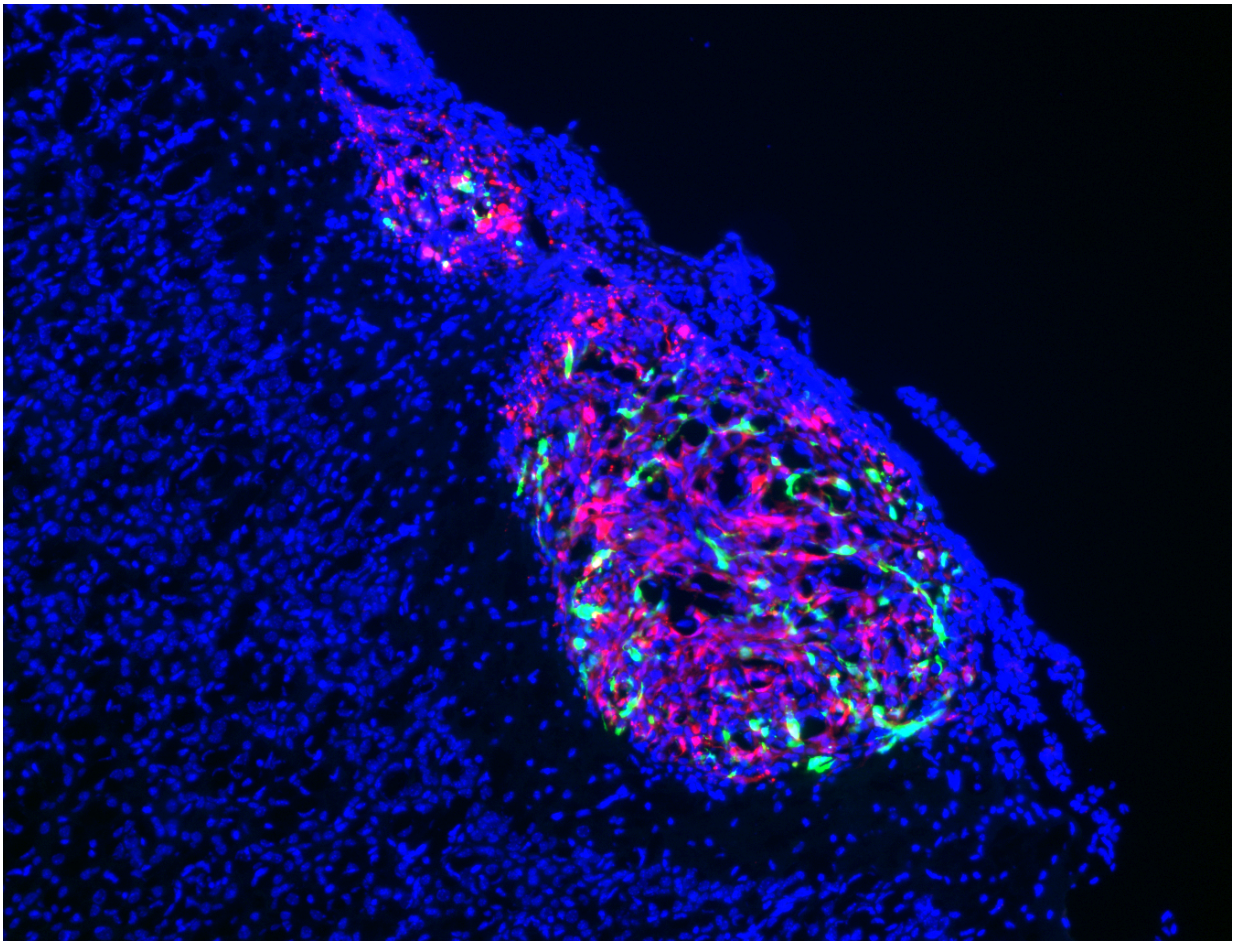
Gene therapy against brain cancer

May 13 2016



Glioblastoma cells. Credit: SISSA

Only a few days ago, the press (especially in English-speaking countries) enthusiastically announced the publication of a study that described in great detail the genetics of breast cancer, a discovery that according to

many marks a breakthrough in the battle against this cancer. This kind of news confirms the impression that in the near future the war against cancer will be fought on the battlefields of genetics. Italy too, is working on this front.

At SISSA, for example, where Antonello Mallamaci and his group have just published highly promising results on the application of gene therapy against glioblastomas, a family of brain tumours among the most common and aggressive. A diagnosis of glioblastoma is literally equal to a very imminent death sentence: "surgery is rarely curative, as these tumours insinuate themselves in healthy tissues, and also chemo- and radiotherapy have little effectiveness. In a short while, very aggressive recurrences develop and that marks the end" explains Antonello Mallamaci, SISSA professor who also collaborates with the Telethon Foundation. "Our approach is radically different: we introduce an additional copy of a given gene into the tumour cells so as to impair their reproductive capacity and lead them to suicide".

The idea for this study came to Mallamaci - who is not an oncologist - after years of close investigation of a particular gene called Emx2. One of the characteristics of this gene, explains the scientist, is to inhibit proliferation of astrocytes during embryonic growth. Glial cells, including astrocytes, are part of the nervous system, where they nourish and protect neurons and finely regulate their function.

"We know that during the early stages of development of the nervous system only neurons grow, whereas glial cells only start to proliferate when neuronal growth is practically complete", explains Carmen Falcone, SISSA research scientist and first author of the paper. "In our previous studies we discovered that Emx2 is expressed at very high levels during the neuronal generation phase, whereas its action declines dramatically when the glial cells start to grow. So the gene keeps astrocyte growth in check up to a certain point".

If it can block astrocytes, why not try and use it to block glioblastomas? "These tumours share many features with astroglia" comments Mallamaci, "hence the idea to use them to our advantage. With the contribution of IST in Genoa, which supplied us with cultures of various types of glioblastoma, we started doing some in vitro tests". And these tests went "beyond our rosiest expectations", explain Falcone and Mallamaci: "in nearly all of the samples, the tumour tissue literally collapsed in less than a week.".

At this point the study continued in two directions. The team first modelled in vitro the molecular mechanisms intervening between when the therapeutic gene is "switched on" and the final effect, finding that the gene attacks tumour metabolism at no less than six points, a result defined as "very robust" by the researchers.

A Trojan horse inside the tumour

After the in vitro studies, the group started its first in vivo experiments on mice, adopting all due precautions to prevent unacceptable suffering of the animals. "So, to prevent damage to the healthy cells, neurons and astrocytes, we selected a specific 'promotor', a piece of DNA that causes the therapeutic gene to become activated only in tumour cells, without attacking the other cells, and we replicated the same result as seen in the first in vitro tests".

Gene therapy is based on the insertion of ad hoc genes into a host cell's genome so that these genes can function inside the cell by borrowing its genetic machinery. How is a bit of genetic code added to a living cell? Scientists use the mechanisms naturally adopted by viruses. Viruses are strange entities: although they have their own genome, they are not able to duplicate, and reproduce, by themselves. For this reason they sneak into cells, and insert their own DNA into the host genome, so that the cell starts working for them by duplicating their genes as well and

forming other viruses. "By making the virus harmless, that is, by emptying the shell containing its genome and filling it with therapeutic genes, we can add new genes, or enhanced versions of endogenous genes, to the host cell", explains Falcone.

So that is precisely what Mallamaci and colleagues did: they introduced a particularly active version of Emx2 into the tumour cells. The results so far have been unequivocal and have demonstrated that Emx2 is able to kill the cells of at least four different types of glioblastoma, both in vitro and in vivo in rodents, without damaging the healthy cells of nervous system. Since they also observed that the treatment targeted may points of the tumour process, there are good chances of effectively contrasting the development of aggressive recurrences. "For these to form, there has to be a process of selection of the strongest tumour cells. By targeting them at a variety of different points, we raise the standards in this selection process and - hopefully - we prevent the recurrences", concludes Mallamaci. "Now we plan to extend the in vivo tests to other glioblastomas. With a lot of hard work and a bit of luck we hope that in a few years' time all this can translate into a tangible benefit for the unfortunate patients afflicted by this disease".

Provided by International School of Advanced Studies (SISSA)