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Survival of the fittest: how brain tumours adapt through complex ecosystems

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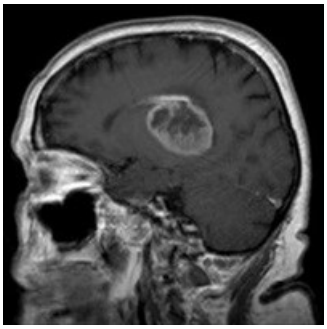
Despite advances in medical technology and a constantly evolving understanding of the mechanisms of cancer progression, researchers and clinicians are faced with a litany of challenges along the road to finding a cure for the most aggressive forms of cancer. This is particularly true of glioblastoma multiforme, the most common and most aggressive form of human brain cancer.

Glioblastoma is universally fatal. Some of the most destructive hallmarks of these tumours, such as uncontrolled and invasive growth into healthy tissues, make this form of brain cancer very difficult to treat. Left untreated people affected typically survive only a few months. The current gold standard for treatment is a combination of surgery, chemotherapy and radiation therapy, but this rarely extends the patients' survival beyond two years as more resistant tumours always grow back. The ability for cells to adapt, evolve and evade allows hardier tumour cells to develop defence mechanisms against conventional treatment.

Cancer cells are as unique as snowflakes

To understand how glioblastoma tumours can evolve to become more resistant, it's important to recognise brain tumours not as uniform tissues, but as complex populations of diverse, dynamic and transforming cell types.



Glioblastoma multiforme. Hellerhof, CC BY-SA

In healthy tissues, a coordinated system of molecules tightly regulates the rate of cell division and expression of genes in response to environmental cues. In cancer cells, this machinery becomes compromised and the cells begin dividing uncontrollably and build up genetic mutations. As the cells reproduce, the genetic identity of the offspring evolves with each new division.

We're also finding more and more evidence that glioblastoma tumours are maintained by a small cache of cancer stem cells. These are slowly dividing, hardy cells which are capable of transforming into many different cell types under the right conditions and rebuilding tumours with new cells of diverse genetic profile.

Many of these cell types possess traits for survival. Rapidly dividing cells can escape surgical treatment, for example, by growing and replicating deeper into the brain where a more permissible environment allows for them to expand with fewer threats to their well-being. These escapee cells often diffuse across the brain by hijacking and migrating along the blood vessels. This invasion and migration places a buffer of healthy tissue between the tumour mass and the surgeon's scalpel.

Surgery can also be resisted through a process known as angiogenesis, which is the production of new blood vessels signalled by tumour cells to secure new nutrition supply lines. Many cells within the tumour possess a toolbox of genes to signal for these new supplies.

Some brain tumour cells also express genes such as MGMT, which grants the ability to repair chemotherapy-induced DNA damage and bypass programmed cell death. Considering that temozolomide, the current drug used to treat glioblastoma, works by damaging DNA through a process known as methylation, cells that are MGMT-positive can resist the drug's effects. As easily exposed tumour cells and those which are sensitive to drugs and radiation are weeded out, cells with these survival traits are selected for expansion and can become the dominant cell type within a tumour mass.

Tumours are rowdy ecosystems

By comparing the tumour landscape to an ecosystem, we can apply an evolutionary model of adaptability, environmental pressures and selection. In an ecosystem, numerous species of plant and animal life compete for limited resources, maintaining a dynamically shifting balance of power. If we interfere with one species, a competitor may inherit a greater share of the resources and have more room to spread out.

We're used to thinking about environmental ecosystems, but cancer has one too.Pierre Pocs Photography, CC BY-SA

These principles can be applied to the tumour habitat, as different cancer cell types compete for space within the brain. Similarly, cells within a tumour ecosystem follow patterns resembling the Darwinian model of natural selection. Dividing cells may produce offspring with mutations that equip them with tools to promote the production of new blood vessels and divide more rapidly. This grants them a competitive edge to secure resources and successfully reproduce.

Next generation treatments

An updated understanding of the brain cancer environment may promote the discovery of nuanced treatment options in the future. One such strategy would be to minimise tumour evolution by keeping cells in a slowly dividing and treatment-responsive state rather than targeting them for general eradication. For this strategy to be realised, clinical researchers could investigate new ways to halt glioblastoma progression by homing in on, and tampering with, the machinery which allows tumour cells to adapt in their ecosystem.

A recent study used computer models of genome maps from the Cancer Genome Atlas Project to identify targets such as ERBB2 or EGFR for which cancer drugs or treatments are already currently available or undergoing clinical trials. Many of these targets are well known in cancer research as tools exploited by tumour cells to develop a competitive advantage.

Focusing on these targets may present an opportunity to block the signalling capabilities for more aggressive traits without killing the cells and providing more space for a challenger. This would essentially de-fang a portion of tumour cells without seriously unbalancing the ecosystem.

A number of exciting developments have been made in the area of immunotherapy and personalised medicine through whole-genome sequencing, but this technology is very much in its infancy. A strategy in which the glioblastoma cell population is kept lazy and placated rather than rowdy and competitive may complement current treatments to improve the quality of life for patients. Such an approach could buy patients a few more years while we develop and refine the next generation of treatment.

ABOUT THE AUTHOR

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