WEAPONISING BISPECIFIC ANTIBODIES TO TACKLE GLIOBLASTOMA

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Abstract

Mini review

BACKGROUND: Glioblastoma is amongst the most common and most aggressive types of brain cancers. The tumour cells are highly malignant and often recur after treatment. Due to its location, it is out of reach for most therapies, rendering it virtually resistant. It is currently impossible to cure patients. With the standard treatment, less than 3-5% of patients survive longer than five years.
OBJECTIVE AND METHODS: By evaluating the current developments in tumor immunology, a targeted therapy that is specifically aimed at tumour cells, ideally with no collateral damage, is discussed.
RESULTS: In glioblastomas, multiple mutations are known. Unfortunately, driver mutations specific for all types of glioblastoma have yet to be identified. Receptor tyrosine kinases, like EGFR, VEGFR and PDGFR, seem to be promising targets for therapy. Nevertheless, any drug against glioblastoma needs to be able to cross the blood-brain barrier (BBB).
CONCLUSION: A bispecific antibody with two active sites could be developed, which independently aid in crossing the BBB and targeting glioblastoma cells. In addition, a toxic compound, attached to the bispecific antibody, could be employed to tackle tumour cells upon binding. With this strategy, future glioblastoma patients can possibly be cured.

WHAT'S KNOWN: It is possible for bispecific antibodies to cross the BBB. Furthermore, targeting glioblastoma cells specifically by binding to their characteristic membrane molecules is possible, e.g. overexpressed or mutated EGFR.

WHAT'S NEW: Bispecific antibodies that can both cross the BBB and specifically target tumour cells in glioblastoma, bear the promise of giving patients a longer life expectancy and better prognosis.

KEYWORDS: blood-brain barrier, targeted therapies, brain cancer, targeted drug delivery, tumor immunology

Glioblastoma

Glioblastoma is the most common and aggressive cancer that commences in the brain. The incidence increases with age, affecting more men than women. Glioblastomas are highly malignant and often recur after treatment [1]. Radiotherapy and surgical resection are therapies that are difficult to apply in glioblastoma because of its diffuse, infiltrative growth into the surrounding brain tissue. Currently, standard treatment consists of radiotherapy followed by a daily dose of the cytostaticum temozolomide [2]. Using this therapy, however, less than 3-5% of patients survive over five years. For the time being, curing patients is impossible [1].

Glioblastoma cells are often supported by an extensive network of blood vessels, allowing them to proliferate rapidly [1]. Glioblastoma cells originate from astrocytes. The exact function of astrocytes is not yet fully identified, but it is known that they only appear in the central nervous system and are essential for the brain to function [3]. Astrocytes are often referred to as the support of neural cells in the brain, but researchers suggest that astrocytes also play an important role in potassium buffering, pH control mechanisms, cell signaling, glutamate and GABA uptake, control of cerebral blood flow, water transport, lactate shuttling, antioxidant functions and perisynaptic processes [4].

Targeted Therapy

The development of cancers is a complicated, multistep process. The first step of this process entails the accumulation of mutations in the DNA of some cells, eventually turning them into cancerous cells. However, not all acquired mutations contribute to the development of cancer. Mutations that do not lead to phenotypic changes are merely present due to faulty gene repair and are termed 'passenger mutations'. On the other hand, the mutations that drive the transition from a healthy cell towards a tumour cell are aptly named 'driver mutations' [5]. Passenger mutations have no prognostic value, even though they are abundant in rapidly proliferating tumour cells. Driver mutations are more rare in tumours, but are compelling targets for therapies [5].

To deal with glioblastoma in patients, it is important to develop a therapy that is specifically targeted at the tumour cells, yet causes little to no harm to the surrounding healthy brain tissue. Such a therapy could be aimed at specific genes, pathways, or cell surface receptors that are abnormally expressed on glioblastoma cells. Several mutations in glioblastomas are known. Unfortunately, a driver mutation that is both specific to and present in all types of glioblastomas, has not yet been discovered [1]. Nonetheless, a couple of genes and pathways with considerable impact on the development of glioblastomas have been identified. Receptor tyrosine kinases, like EGFR, VEGFR and PDGFR could be used to specifically target the glioblastoma cells [6]. Moreover, IDH1, an enzyme part of the TCA cycle in glucose, is often mutated in glioblastoma and expressed in MHC class I on the cell surface. While also present in normal brain cells, EGF receptors and IDH1 are mutated in 70% and 90% of primary and secondary glioblastoma patients, respectively [7, 8]. Therefore, they offer the possibility to distinguish between tumour cells and normal cells.

Blood-brain Barrier

Any drug targeting glioblastoma needs to be able to cross the blood-brain barrier (BBB), since direct injection in the brain is not preferred due to safety concerns, such as risk of infection and the vulnerability of the brain. The blood-brain barrier is the barrier that prevents compounds from the blood circulation to go straight into the brain. The BBB con-

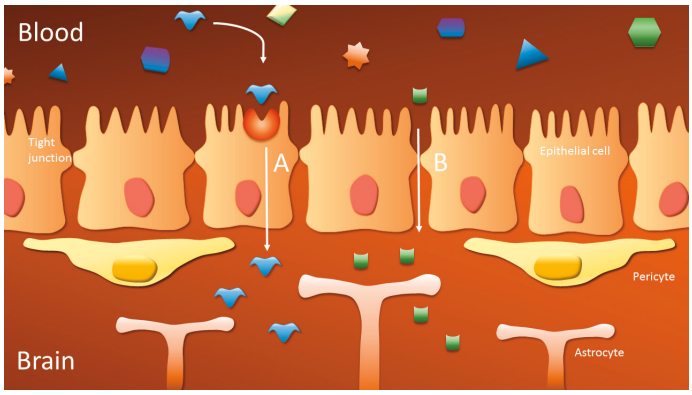

Figure 1: *Schematic depiction of the blood-brain barrier. The upper part of the figure shows the blood vessel and the lower part shows the brain area, the middle part shows the barrier. Route A shows how substances can go through the barrier by using transporters on the cell membrane of the epithelial cells. Route B shows that some very small compounds are able to pass the barrier by passing the tight junctions.*

Figure 2: *Schematic depiction of a bispecific antibody that could be used to treat glioblastoma. The bispecific antibody consist of two regular antibodies attached to each other via a connective molecule. The part responsible for transportation over the BBB is depicted in red, the part that recognises the tumour cells in blue. Shown in black is the connective structure keeping the two antibodies together. The orange sphere represents the toxic agent, responsible for killing the tumour cells.*

sists of three main cellular elements: endothelial cells, astrocyte endfeet and pericytes (figure 1). Tight junctions between the endothelial cells prevent compounds, especially hydrophilic molecules, from entering the brain directly. The basal lamina of the endothelial cells is also important for the BBB, since it forms yet another physical barrier between the blood and the brain [9].

There are, however, mechanisms to make specific compounds able to cross the BBB. For example, the brain needs nutrients such as glucose, iron and amino acids for numerous cellular activities. These nutrients are not able to cross the BBB spontaneously. To facilitate the transportation of these nutrients, specific transporters are present on the cell surface of the cerebral endothelial cells. Whereas small lipophilic compounds, such as O2 and CO2, are able to diffuse freely across the BBB to driven by their concentration gradient [9]. Of course, transportation is not limited to the molecules listed here, as others are indispensable to normal brain functioning as well. Given this restrictive nature of the BBB, it is hard but not impossible to target diseases that are located in the brain with drugs [9].

Bispecific antibody

Bispecific antibodies are artificially made antibodies that are able to specifically bind to two distinct targets. This is possible because of their two different variable antigen-binding sites (Figure 2) [10]. By binding two different targets, it should be possible to make a compound that can bind a receptor on the BBB in order to reach the brain (similar to route A in figure 1). The other binding site of the antibody could, once it has passed the BBB, bind to the tumour cells. Moreover, a specific toxic sphere could be added that kills the tumour cells after the bispecific antibody has reached its target. This technique could be used to develop a drug that is able to specifically target the glioblastoma cells.

Discussion

Patients diagnosed with glioblastoma have a poor prognosis, because the current treatment is unable to successfully target the tumour cells located in the brain. The main problem in treating glioblastomas is the inability of effector molecules to pass the BBB in order to reach the tumour cells. This renders almost all commonly used anticancer drugs useless for treatment of glioblastomas. A medicine mimicking glucose, iron or certain amino acids, could be carried over the BBB using transporters on the cell membrane of the epithelial cells that make up the BBB. Another difficulty when developing an innovative therapy for glioblastoma, is finding a specific molecule to target the tumour cells. EGF receptors and IDH1 could be suitable targets to differentiate between tumour cells and normal cells. A targeted therapy aimed at such molecules can reduce the damage to tissue surrounding the tumour and thereby reduce complications resulting from the treatment.

The ultimate goal is to find a medicine that is able to cross the BBB and selectively tackle the glioblastoma cells at the same time. Bispecific antibodies that specifically recognise both the tumour cells and a receptor that facilitates its transportation over the BBB appear to be promising to achieve this. A cytotoxic agent could be attached to the bispecific antibody, which should only be activated upon tumour cell recognition and binding. Using this approach, it could be possible to cure glioblastoma patients in the future.

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