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Perspective

Glioma-related edema: new insight into molecular mechanisms and their clinical implications

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Abstract

Glioma-related edema (GRE) is a significant contributor to morbidity and mortality from glioma. GRE is a complicated process involving not only peritumoral edema but also the water content of the tumor body. In terms of etiology, this condition derives from both GRE in the untreated state and GRE secondary to clinical intervention, and different cell types contribute to distinct components of GRE. Peritumoral edema was previously believed to loosen glioma tissue, facilitating tumor-cell invasion; however, the nutrition hypothesis of the tumor microecosystem suggests that tumor cells invade for the sake of nutrition. Edema is the pathologic consequence of the reconstructed trophic linkage within the tumor microecosystem. Glioma cells induce peritumoral brain edema via an active process that supplies a suitable niche for peritumoral invasive cells, suggesting that glioma-related peritumoral brain edema is determined by the invasive property of tumor cells. There are differences between pivotal molecular events and reactive molecular events in the development of GRE. Molecular therapy should target the former, as targeting reactive molecular events will produce undesired or even adverse results. At present, brain glioma angiogenesis models have not been translated into a new understanding of the features of brain images. The effect of these models on peritumoral brain edema is unclear. Clinical approaches should be transformed on the basis of new knowledge of the molecular mechanism underlying GRE. Exploring clinical assessment methods, optimizing the existing control strategy of GRE, and simultaneously developing new treatments are essential.

Key words Glioma, edema, invasion, translational medicine

Cerebral edema is swelling caused by abnormal accumulation of water in the brain parenchyma. Glioma-related edema (GRE), especially peritumoral brain edema (PTBE), is seen commonly in the clinic. GRE promotes glioma cell invasion [1,2] and significantly influences glioma prognosis. Indeed, glioma prognosis may be independently predicted by appropriately identifying the degree of peritumoral edema on magnetic resonance images (MRI) of the brain[3,4]. PTBE also impacts patient cognition[5] and therefore should be taken into consideration when planning the target area for radiotherapy[6]. In general, PTBE is associated with an incomplete blood-tumor barrier and excess tissue space arising from aberrant metabolism of water in tumor tissue. This results in accumulation of a large volume of liquid and soluble components of the blood plasma. Recent advances in molecular biology have enabled the identification of basic molecular mechanisms underlying GRE, but many issues still remain to be resolved. Only with deeper investigation of the molecular mechanism can we work out more effective strategies for controlling GRE. Here we review advanced studies on the molecular mechanisms of GRE and their clinical implications.

Defining and Classifying GRE

In the past, GRE conventionally referred to PTBE, though there was no indication that this swelling affected a specific region in the brain tissue. Indeed, GRE includes the water content in the tumor tissue and in the peritumoral space. Identifying edema of glioma is

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extremely complex in clinical practice; it includes not only GRE diagnosed in the untreated state but also the GRE arising after clinical intervention.

Different types of GRE result from complex and dynamic interaction among all types of cells in edema region—glioma cells, vascular endothelial cells, neuroglial cells, and microglial cells [7-9]. Glioma cells are responsible for edema in the untreated glioma state, whereas vascular endothelial cells induce angioedema as well as acute, subacute, delayed, and pseudoprogressive relative brain edema that emerges after radiotherapy [8]. Different types of GRE may be caused by common or distinct molecular events, such as vascular endothelial growth factor (VEGF) events[10,11] and cyclooxygenase-2 (Cox-2) events [9].

The involvement of specific cells and molecular events gives each type of edema a distinct molecular mechanism, and therefore, each type may have a distinct therapeutic implication and patient outcome implication[8,9]. However, such a difference has yet to be observed. Therefore, the classification of GRE must be better defined before studying the molecular mechanism of GRE.

The Nature of GRE Diagnosed in the Untreated State

GRE, especially PTBE, has been historically considered a typical vasogenic cerebral edema, which corrects the past fault in recognizing that edema fluid is the product of tumor tissue secretions. The formation of GRE involves numerous molecular mediators, including VEGF, aquaporins (AQP), Cox-2, inflammatory mediators, nitric oxide (NO), and the tight junction relative protein between capillary endothelial cells. The latter also comprises other protein families like claudins, occludins, junction-associated molecules (JAM), and zonula occludens (ZO).

The pivotal and most widely studied mediator is VEGF. Studies show that VEGF down-regulates the expression or structure of tight junction proteins, which results in enhanced vascular permeability by enlarging the cleft between endothelial cells and the fenestra of segmental endothelial cells[12]. A recent study suggests that the content of vesiculo-vacuolar organelle (VVO)-like structures in the tumor vessel endothelial cytoplasm is associated with both the severity of edema and the VEGF content in tissue; however, the severity of edema and the VEGF content in tissue have no distinct relevance to microvascular fenestra or the cleft between endothelial cells. We hypothesize that the increase in VVO-like structures of endothelial cells augments vascular permeability, which may lead to tumor edema and PTBE[13,14]. Obviously, the process wherein vascular permeability increases by the increasing fenestra and cleft among endothelial cells is analogous to leakage, which is a passive process. However, the process of increasing vascular permeability by increasing VVO-like structures is similar to pumping out. According to the nutrition hypothesis of the tumor microecosystem, the tumor invades for the sake of nutrition [15]. Edema is the pathologic consequence of the reconstructed trophic linkage within the tumor microecosystem[14]. At this point, the process by which glioma cells induce PTBE is active, supplying a suitable niche for peritumoral invasive cells. This suggests that glioma-associated PTBE is determined by the invasive property of tumor cells.

Peritumoral edema was formerly thought to loosen tissue, which is favorable for invading tumor cells [16]. However, several studies show that the anti-angiogenesis activity in glioma would significantly inhibit cerebral edema, yet would generate more extensive invasion[17,18]. This phenomenon support the speculation that tumor cell invasion is in order to get the nutrition [15] and that PTBE supplies a suitable niche (trophic niche) for peritumoral invasive cells.

Distinguish Pivotal Molecular Events and Reactive Molecular Events Taking Place in the GRE

A potential strategy for controlling GRE is molecular targeted therapy. However, studies of the molecular mechanism of GRE usually have different and even opposing results. For instance, some studies in high-grade astrocytoma and glioblastoma multiforme suggest that AQP4, the expression of which is positively correlated with the degree of tumor edema, increases dramatically within tumor cells and the cytoplasm of peritumoral reactive glioma cells[19,20]. While other studies show that the expression of AQP4 is not consistent with pathologic grade, the expression of AQP4 in grade I and grade IV glioma was distinctly higher than that in grade II glioma[21].

APQ4, which is expressed at the brain-CSF interfaces and astrocytic end feet, maintains cerebral water balance and exhibits a polarized pattern. In normal brain tissue, APQ4 is limited to the astrocyte foot processes around cerebral microvessels and generates a limit for glial membranes. However, the distribution and expression of APQ4 in pathologic conditions are abnormal, which results in cerebral edema[22]. Our previous notion was that AQP4 protected neurons, maintaining the acid-base and osmotic pressure balance [23], but recent studies show that abnormal APQ4 expression is usually accompanied by expression changes of other molecules that are related with cerebral edema, such as up-regulation of VEGF and down-regulation of occludin[24,25].

The study of VEGF and AQP4 in glioma revealed that up-regulation of APQ4 occurs in response to edema induced by VEGF[26], which confirms that AQP4 protects against vasogenic cerebral edema and exacerbates cytotoxic cerebral edema[27,28].

Taken together, VEGF and APQ4 are pivotal molecular events and reactive molecular events underlying GRE, respectively. Undoubtedly, targeting reactive molecular events as therapies will produce undesired or even adverse results. So, it is important to understand the functions of specific molecular event from the holistic molecular events taking place in the GRE.

Translating the New Understanding of the GRE Molecular Mechanism to the Clinic

Clinically, GRE is primarily analyzed by imaging, especially MRI, which provides the basis of strategy formulation and prognostic assessment for glioma patients. However, little is known about how to merge the evolving knowledge of brain imaging and the molecular mechanisms of GRE. For example, GRE refers mostly to vasogenic cerebral edema, which is primarily characterized by microcirculation abnormalities. Recent studies have found that at least five mechanisms by which gliomas achieve neovascularization have been described: vascular co-option, angiogenesis, vasculogenesis, vascular mimicry, and (the most recently described) glioblastoma-endothelial cell transdifferentiation[29]. Some researchers also think vascular mimicry formation impacts brain glioma prognosis[30]. Nevertheless, brain glioma angiogenesis models have not been translated into a new understanding of image features. What effect do different brain glioma angiogenesis models have on peritumoral brain edema? What are the differences among the distinct blood-tumor barriers of brain glioma angiogenesis models? What effect do the differences in glioma angiogenesis models have on image enhancement scanning characteristics? These questions have not yet been answered.

Based on the consensus of expert neuro-oncologists, glucocorticoids are the first-line medication for PTBE[1,31]. Although glucocorticoids rapidly and efficiently reduce brain GRE, the mechanism of their anti-edema effect is still unclear. Generally, they are believed to evoke a curative effect by reducing the permeability of the damaged blood-brain barrier. Glucocorticoids, such as dexamethasone, may exert their role through inhibiting vascular permeability factor. Mannitol, a classic drug for reducing cranial pressure, has been widely used to treat GRE, especially acute cerebral edema and brain hernia. However, for mannitol to induce an anti-edema effect, the blood-brain barrier must function normally. Because the blood-tumor barrier of glioma is abnormal, long-term use of mannitol may be accompanied by mannitol leakage to the interstitial space, leading to aggravated late-onset edema. At present, a number of drugs are under investigation for treating GRE, including adrenocorticotropic hormone, Cox-2 inhibitors, and VEGF antibody.

Conclusions

Glioma-related edema (GRE) is seen commonly in the clinic. Glioma cells induce peritumoral brain edema via an active process that supplies a suitable niche for peritumoral invasive cells. There are differences between pivotal molecular events and reactive molecular events in the development of GRE. A potential strategy for controlling GRE is molecular targeted therapy. Clinical treatment for GRE will be transformed as we better understand its molecular mechanisms. Exploring new methods of clinical assessment, optimizing existing strategies to control GRE, and simultaneously developing novel treatments are essential.

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