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Disparity of Cell Death Attributes in Primary Adult Human Glioblastoma: A Review

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Abstract

Primary adult glioblastoma is a malignant tumor of the neuroaxis, throughout which it will spread widely. The survival rate of the patients is inferior to 15 months. A poor outcome is related to drug resistance, as well as to the blood-brain-barrier permeability. A major mechanism of the drug impediment is based on an apoptotic blockade, but also, increasingly, of nonapoptotic cell death, the various forms of which may be manipulated to a level that may initiate some degree of improvement in the clinical features. But these molecules, for example, those responsible for autophagic or paraptotic cell death, have reacted so far by obscure processes that are just starting to be elucidated. The goal of this review is to display the diverse variants of cell death involved in glioblastoma and to highlight the relevance of molecules and processes to the mechanism and therapy of this malignancy. Moreover, attempts will be made to trace the data concerning the repair manipulations performed on the original defects inherent in this cancer.

Keywords: Adult Glioblastoma, Apoptosis, Antidepressants, Curcumin, Autophagy

Introduction

Glioblastoma (gbm), the most common and aggressive, relapsing and mostly lethal tumor of the central nervous system, is yet to anticipate an efficacious healing. The apoptotic and non-apoptotic cell death modulations are put forward to overcome the apoptotic blockade which curbs the efficacy of temozolomide (tzm), the advanced chemotherapeutic agent of choice for gbm therapy. Although further mechanisms of obstruction to a successful treatment of gbm are mentioned, the multi-purpose means of triggering, employed by cell death handling, is hereby scrutinized [1,2].

Materials and Methods

The present manuscript starts by summarizing three of our papers, that have recently addressed part of the issues of concern.

A review of the papers dealing with the association between glioblastoma developing primarily in adult human beings and diverse forms of cell death is presented. Included, are apoptosis (Figure 1), as well as distinct non-apoptotic cell death variants. The relevance of the mechanisms of cell death variants, to the biology, and, especially, on the response to therapy, in glioblastoma are reviewed (Figure 2).

A few types of non-apoptotic cell death were excluded from the review, notably, necroptosis, ferroptosis, pyroptosis and disulfidptosis, since they have been described only recently. The later cell-death forms are expected to represent an attractive topic of discussion, in a few years' time.

Figures 1: Falling Leaves by Apoptosis.

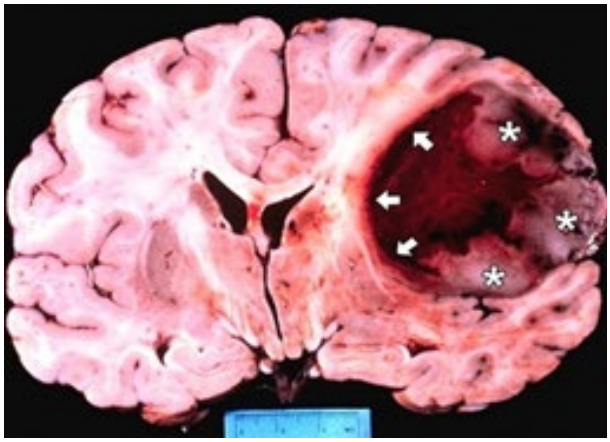

Figure 2: Glioblastoma. Prominent Cystic Necrosis.

Cell Death and Glioblastoma

Vdac1 in Glioblastoma

Our first review paper mentioned a role for gbm with the voltage-dependent anion channel 1 (vdac1), a mitochondrial protein in control of cellular energy and metabolism. Moreover, the vdac1 contributes to the dissemination of apoptotic factors from mitochondria, equally affecting apoptotic-controlling elements [2].

Traumatic gbm

Our recent commentary [3] has again assessed whether head trauma may be relevant to the initiation of the gbm. While reviewing ewing's and his successors' criteria in this context, we were able to suggest that the restrictive conclusions reached by these scientists were overtly limited. The article further identified three transcription factors that may correlate with traumatic brain injury (tbi). Hereby, the above elements encompassed p53, hypoxia-inducible factor (hif-1α) and c-myc.

P53 may induce neuronal apoptosis and evoke regeneration after tbi by initiating a p53-induced death domain protein [4]. Hif-1α may promote the regenerative healing of tbi. It is expected to repair the blood-brain barrier impediments that follows tbi [5]. C-myc is required for p53-dependent apoptosis, incidental to dna disruption [6].

Glioblastoma in Schizophrenia

A more recent review of ours reconsidered the inverse association between the incidence of schizophrenia (scz) and gbm. It was suggested that similar tumor suppressor genes have been identified in both these conditions. The findings were highlighted by studies using psychiatric medicines, which may directly account for the low incidence of gbm in scz. Three groups of psychiatric medications relate with a low incidence of gbm:
A. First generation anti-psychotic medications-chlorpromazine and haloperidol.
B. Second generation anti-psychotic drugs-aripiprazole and olanzapine.
C. Antidepressants–fluoxetine and escitalopram. In addition, a mood modulator, valproic acid may affect the gbm outcome.
A brief investigation, carried out among physicians from various disciplines at our hospital, has implied that not even one of our physicians had been aware of the inverse relationship described above between scz and gbm [7].

Glioblastoma and Cell Death Variants

Glioblastoma is manifested among other validations of cell multiplication, by necrosis, by marked hindrance to apoptosis, as well as by a genomic disarray [8]. The generation of type i cell death (caspase-induced apoptosis) is at the bottom of destruction of tumor cells by chemotherapy and/or radiotherapy (figure 3). Indeed, the poor prognosis prevailing in the vast majority of gbm patients is highly associated with apoptosis resistance (Figure 4) [9]. To overcome the apoptotic handicap, several processes have been proposed. One of the most inspiring involves a few plant-derived substances that may activate apoptosis-associated mechanisms, as a cell cycle disruption in gbm tumor cells. In this category of plants, we recognize curcumin, ephod, caffeine, and dipotassium glycyrrhizinates, activated in part via microrna modulation [10]. Another phyto-molecule, effective against malignant growths, will induce, among others, cellular apoptosis. This substance, called berberine, may have a significant role with these processes, in gbm [11].

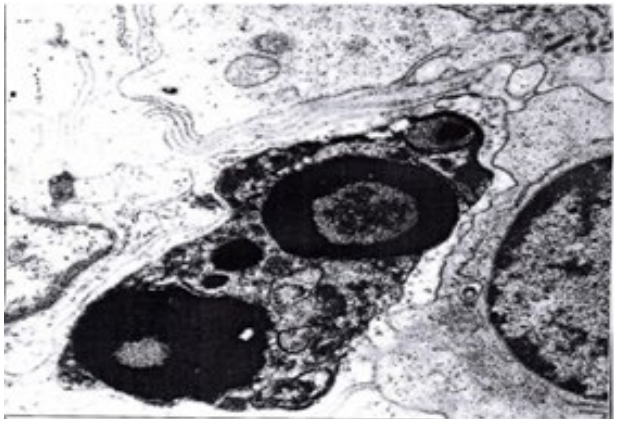

Figure 3: Em Micrograph of H-Reed-Sternberg Apoptotic cell. Note Condensation of the Nuclei, and Dissociation of other Organelles. Uranyl Acetate, Lead Citrate x 10,000. (Benharroch et al, 1996).

Figure 4: Ppt title: Diversity of Cell Death.

Curcumin has been recently found to play a multi-variables role in gbm, encompassing cell proliferation, apoptosis, autophagy, paraptosis, cell cycle arrest, oxidative stress, and tumor-cell motility. Curcumin will affect gbm, among other cancers, via activation of p53, mapk, p13k/akt, rb, jak/stat and of nf-κb regulation [12,13]. Additional natural compounds are displayed for their capacity to enhance the archetype of the gbm chemotherapeutic agent, tmz. In most gbm patients, tmz is inadequate for blocking tumor proliferation and metastatic spread. Consequently, the cancer reverts its course and relapses. The molecules added to tmz to prevent a gbm relapse, include, tea tree oil, lactoferrin, aloe-emodin and harpoon. These compounds were assessed so far, with a gbm cell line, u87mg, as well as with a murine animal model, only [14]. Prior mention has been made of the apoptotic induction of anti-gbm therapeutic agents. We hereby comprise the role of non-coding rnas as well as of micro-rna on apoptosis, to improve the chemotherapeutic impact on the tumor [15].

Autophagy and Glioblastoma Treatment

A vastly mutated genome may account for the obstruction of gbm on inducing an effective treatment. Of note, the survival rate of this malignant tumor is below 15 months. Since apoptosis is defective thereof, one may propose a non-apoptotic cell death modulation, like the one related with autophagy, for the disposal of gbm cells.

However, in malignancies, autophagy might induce either cell death, or possibly, survival of the tumor cell. To promote death by autophagy, the use of both autophagic inducers as well as autophagic inhibitors becomes necessary [16].

But our grasp on autophagic mechanisms remains very partial. Glioblastoma clinics still display a pejorative survival. A possible reason is the very complex heterogeneity of this malignant tumor. It is suggested to combine tmz together with both an autophagic suppressor and with autophagic mediators [17].

Cells from gbm spread to the central nervous system despite progress in diagnostics and treatment, but the tumor still carries out poor results. The reason may be related to the significance of permeability of the blood-brain barrier (bbb). The choice should revert to medicines, that give rise to a high bbb permeability. Antidepressants display such qualities, a few may display gbm cytotoxicity. Some antidepressants–imipramine, maprotiline, fluoxetine, escitalopram, release in addition, autophagy induction. On the other hand, others, like nortriptyline, clomipramine, and paroxetine, have been identified as autophagy inhibitors. Collectively, antidepressants in gbm have raised a relatively promising outcome [18].

A better understanding of the disparity in the role of autophagy in gbm is needed to improve the results of a combined therapy, meaning that of tmz with autophagy modulation (Figure 5) [19].

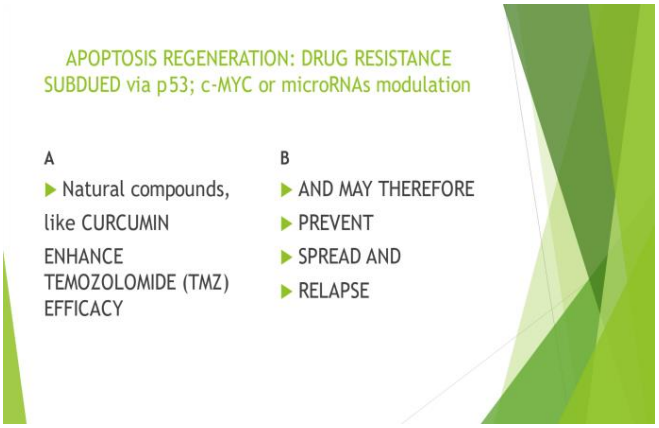

Figure 5: Role of Apoptosis in Glioblastoma Therapy

Necrosis in Glioblastoma

Glioblastoma stands out histologically from low grade astrocytomas, by upgrading necrosis and microvascular proliferation. Necrosis is hereby delimited by pseudopalissades, which predominates in gbm and have a deficient prognostic import. The pseudopalissades conceal severe hypoxia and strongly display hif-1α, as well as vegf and il-8. It is believed that the pseudopalissades express ripples of tumor cells, spreading away from a central focus of hypoxia, and which follows a vascular injury [20].

Hans joachim scherer (1906-1946), a german pathologist, is considered the father of modern neuropathology. He first described "glomerular" structures in gliomas, which, together with the non-resect ability of these cancers, will display pseudopalissading, necrosis and the delayed symptomatology, typical of gliomas [21]. It has been proposed that since hypoxia is the mainstay of gbm, one may engage in a promising new therapeutic avenue by addressing hypoxia and more specifically tackling the role of hif-1α (Figure 6) [22].

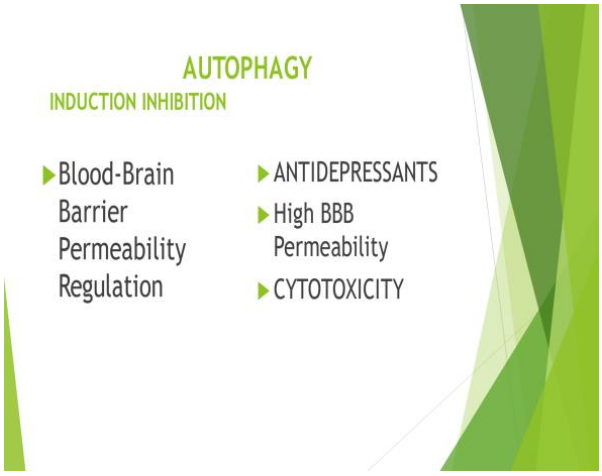

Figure 6: Autophagy Relevance to Blood-Brain Barrier Permeability in Glioblastoma.

The recent who cns 5 classification was established on new concepts, notably by differentiating isocitrate dehydrogenate (idh)-wild type from idh-mutant groups. Thus, gbm is considered to highlight exclusively the idh-wild type, with microvascular hyperplasia, necrosis, telomerase reverse transcriptase promoter mutation, epidermal growth factor receptor gene amplification, +7/-10 chromosome copy number changes (cns who grade 4) [23].

Paraptosis and Curcumin

Glioblastoma exhibits drug resistance and plant extracts are being used increasingly, to overcome this barrier. Curcumin is activated via multiple pathways, including, by paraptosis [12]. The a172 gbm cell line, exposed to curcumin, will induce paraptosis, that is characterized by alterations in the integrity of the endoplasmic reticulum [24]. A small part of the tumor cells will undergo apoptosis with tmz. But, under tmz therapy, most cells will undergo senescence [25]. Senescent cells will produce extensive, chronic secretory changes, which might enhance tumorigenicity and an increased migratory proclivity (Figure 7) [26].

A few kinds of non-apoptotic cell death are excluded from the review, notably, necroptosis, ferroptosis, pyroptosis and disulfidptosis, as they have been defined only recently (Figures 8,9).

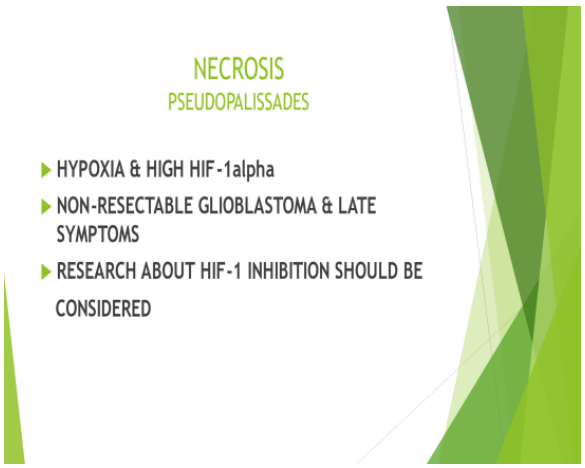

Figure 7: Necrosis and Hypoxia in Non-Resectable Glioblastoma.

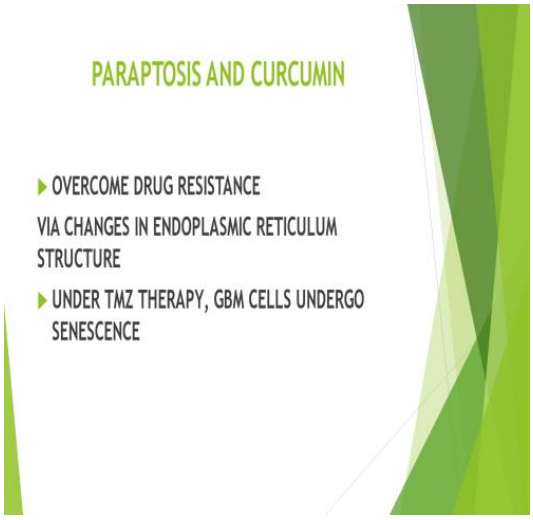

Figure 8: Senescence and Paraptosis.

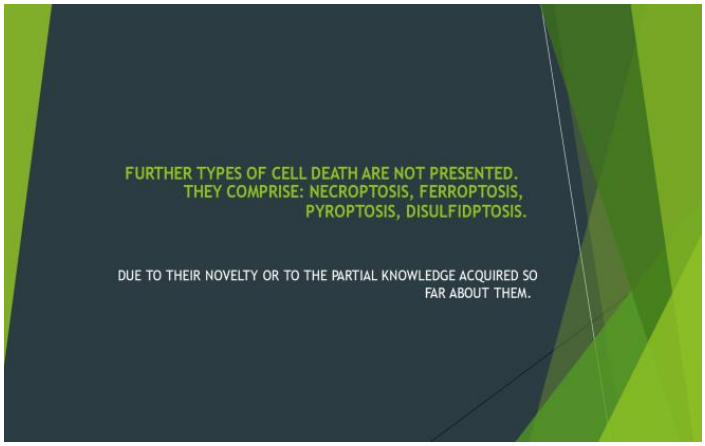

Figure 9: Additional Types of Cell Death in Glioblastoma.

Discussion

Glioblastoma stands out against those malignant tumors which respond more readily to chemo/radiotherapy, by several lines of resistance. Consequently, two or more mechanisms might compile, resulting in a nil response to therapy. Given a general agreement, that tmz is indeed the chemotherapeutic drug of choice to tackle this malignancy, the main obstacle met, is usually the resistance to caspase-induced apoptosis. The system failure is hereby due to the consequent loss of tumor cell destruction by therapeutic agents. A bypass of this obstruction will be expected to induce the reactivation of type i apoptosis. It is proposed that this step be carried out by plant extracts, like curcumin (the most used), caffeine, or newer compounds, like berberine.

Further agents may obtain similar results. They include autophagic molecules, that induce non-apoptotic cell death activation. Their limitation, accounting for the present level of knowledge, will exhibit autophagy that might induce both survival of the tumor cell as well as its death. Ideally, both inhibitors and suppressors of autophagy should collaborate, for cell death to occur.

The complex heterogeneity of gbm does not contribute to an improved survival, but it correlates with autophagic suppressors and autophagic mediators.

Another factor to consider is the bbb, the permeability of which is critical, especially regarding the tumor spread. Antidepressants, in their different forms, are effective in modeling the bbb permeability. Some will play a role as autophagic inducers (fluoxetine), while others act as autophagy inhibitors (nortriptyline).

Moreover, necrosis is critical to survival, especially when presenting with pseudopalissades. In this circumstance, a central nidus of hypoxia will promote the spreading out of tumor cells, centrifugally to the periphery of the necrosis. The hypoxic center is rich in hif-1α.

Another, non-apoptosis cell death type, paraptosis, is also related with curcumin. Its modulation will cause the dismantling of the endoplasmic reticulum. When in addition, tmz is administered, most tumor cells will evolve to senescence. Agglomeration of senescent tumor cells might promote both tumorigenicity and an increased migration of the tumor cells.

Conclusion

One may expect a progression in the efficacy of the chemotherapeutic response to tmz, however, this may occur through very small steps. The modulation of the bbb might probably contribute. A repair of the hypoxia, by blocking the hif-1α, may lead partially to the arrest of the dissemination of the tumor. Hif-1, by overseeing the regulation of oxygen, supervises angiogenesis, erythropoiesis and more. As an inhibitor of this network, hif-1 hinders the function of hif-1α, as well as of vhl. It is expected that the above-mentioned antagonism may re-establish the bbb filtration capacity and, thus, block the spread of gbm cells, thereby, reversing a further aspect of the gbm carcinogenesis [27].

Authors Contribution

DB: Manuscript conception, materials review, redaction, revision of submitted version, paper submission.
YG: Final revision, reading of submitted version and its concurrence.

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Conflicts of Interest

The authors declare 'no conflicts of interest are evident'.

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Informed Consent

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Institutional Review Board Statement

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Data Availability Statement

See: Fathima S, Sinha S, Donakonda S. Network analysis identifies drug targets and small molecules to modulate apoptosis in resistant cancers. Cancers (basel) 2021,13,851

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