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Glioblastoma and chemoresistance to alkylating agents: Involvement of apoptosis, autophagy, and unfolded protein response

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ABSTRACT

Despite advances in neurosurgical techniques and radio-/chemotherapy, the treatment of brain tumors remains a challenge. This is particularly true for the most frequent and fatal adult brain tumor, glioblastoma (GB). Upon diagnosis, the average survival time of GB patients remains only approximately 15 months. The alkylating drug temozolomide (TMZ) is routinely used in brain tumor patients and induces apoptosis, autophagy and unfolded protein response (UPR). Here, we review these cellular mechanisms and their contributions to TMZ chemoresistance in brain tumors, with a particular emphasis on TMZ chemoresistance in glioma stem cells and GB.

1. Glioblastoma: Epidemiology, classification and current management

1.1. Epidemiology

Primary central nervous system (CNS) tumors are a histologically diverse group of neoplasms with over one hundred distinct entities identified in the current World Health Organization (WHO) classification system (Louis et al., 2016). Glioblastoma (GB), a high grade form of diffuse glioma, is the most common malignant CNS tumor in adults, representing 46.6% of cases (Ostrom et al., 2016). The incidence of adult GB increases with age, with a median age of 64 years at diagnosis (Ostrom et al., 2016). The natural history is characterized by rapid, aggressive growth and they are incurable at diagnosis. The outcomes for GB remain poor, with modern therapies resulting in a median overall survival (OS) of approximately 14 months (Stupp et al., 2009), and a 5 year survival of only 5.5% (Ostrom et al., 2016). GB can result in devastating neurological sequelae, with common presenting symptoms including weakness, visual and sensory changes, alterations in mood, memory or executive function, headaches and seizures (Alexander & Cloughesy, 2017). Given their high mortality and relative resistance to conventional therapy, there has been significant interest in improving our understanding of the molecular landscape and optimal treatment of GB.

1.2. Classification

Classically, CNS tumors have been classified microscopically based

Abbreviations: ABCB1, ATP-binding cassette sub-family B member 1; ABCG, ATP-binding cassette drug efflux transporters; ACD, autophagic cell death; AKT, alpha serine/threonine protein kinase; ALDH, aldehyde dehydrogenase; AMPK, AMP-activated protein kinase; AP, apurinic/apyrimidinic; APE, apurinic/apyrimidinic endonuclease; Atg, autophagy-related gene; ATP, adenosine triphosphate; ATF6, activating transcription factor 6; ATRX, alpha-thalassemia/mental-retardation-syndrome-X-linked; BADF, Bcl-2 associated agonist of cell death factor; BAK, Bcl-2 homologous antagonist/killer; BAX, Bcl-2 associated X protein; Bcl-2, B-cell lymphoma-2; BCL-XL, BCL extra-large; BER, base excision repair; bFGF, basic fibroblast growth factor; BFP, 2,4-bis(4-fluorophenylacetyl)phloroglucinol; BG, benzylguanine; BH, Bcl-2 homology; BID, BH3 interacting domain; BIK, Bcl-2 interacting killer; BIM, Bcl-2 interacting mediator; BMI1, B lymphoma Mo-MLV insertion region 1; BMF, BCL-2-modifying factor; BMP, bone morphogenetic protein; BOK, BCL-2 related ovarian killer; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CBP, CREB-binding protein; CD44, cluster of differentiation 44; CDKN2A/B, cyclin-dependent kinase Inhibitor 2A; CHOP, C/EBP homologous protein; c-JUN, cellular V-jun avian sarcoma virus 17 oncogene homolog; CMA, chaperone-mediated autophagy; CaMKII, calmodulin-dependent protein kinase II; c-MYB, cellular avian myeloblastosis virus oncogene cellular homolog; CNS, central nervous system; CQ, chloroquine; CSC, cancer stem cell; CTα, C-terminal peptide mimetic alpha; Cx43, connexin-43; DISC, death-inducing complex; DLL3, delta-like 3; DRD4, dopamine receptor 4; dRP, deoxyribophosphate; DRAM, damage regulated autophagy modulator; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial mesenchymal transition; ER, endoplasmic reticulum; ERK, extracellular signal regulated kinase; ETC, electron transport chain; EZH2, Enhancer of Zeste Homolog 2; FAM134B, Family With Sequence Similarity 134 Member B; Fas-L, Fas ligand; FADD, Fas-associated death domain; FEN1, Flap endonuclease 1; GANT61, small-molecule inhibitor of glioma-associated oncogene 1; GB, glioblastoma; GIC, GB initiating cells; Gli1, glioma-associated oncogene 1; GNS, glioma-derived neural stem cells; GRPs, glucose regulated proteins; GSK3β, glycogen synthase kinase 3β; GSC, glioma stem cell; GTP, guanosine-5′-triphosphate; HCQ, hydroxychloroquine; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; HMGA2, High Mobility Group A2; HR, homologous recombination; ID4, inhibitor of differentiation 4; IDH, isocitrate dehydrogenase; IFN-β, interferon-β; IL-24, interleukin-24; IRE, inositol requiring enzyme; JAK2, Janus kinase 2; JNK, Jun amino-terminal kinases; KFERQ, chaperone mediated autophagy targeting motif; KRAS, Kirsten rat sarcoma; LAMP, lysosomal membrane protein; LC3, 1B-light chain 3; LIG, ligase; LIR, LC3-interacting regions; MA, methyladenine; MAPK, mitogen-activated kinases; MCL-1, myeloid cell leukemia-1; mda-7, melanoma differentiation associated gene-7; MDR, multi drug-resistance; MDR1, multidrug resistance protein 1; MGMT, methylguanine-DNA methyltransferase; mGluR3, metabotropic glutamate receptor 3; MiR-9, microRNA-9; MLH1, MutL homolog 1; MMP, matrix metalloproteinases; MMR, mismatch repair; MPG, methyladenine-DNA glycosylase; MSH, melanocyte-stimulating hormone; MTIC, 3-methyl-(triazen-1-yl) imidazole-4-carboximide; mTOR, mammalian target of rapamycin; mTOR, complex1/2, mammalian target of rapamycin complex1/2; NAD, nicotinamide adenine dinucleotide; NANOG, Nanog homeobox; NCOR2, nuclear receptor corepressor 2; NEO212, a conjugate of temozolomide to perillyl alcohol; NER, nucleotide excision repair; NF1, neurofibromin1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIX, NIP3-like protein X; NLK, nemo like kinase; Notch, neurogenic locus notch homolog protein; NOXA, a pro-apoptotic BH3-only member of the Bcl-2 family; Nrf2, nuclear factor erythroid 2-related factor 2; NSCs, neural stem cells; NVP-BEZ235, PI3K/mTOR inhibitor; Olig2, oligodendrocyte transcription factor; OMM, outer mitochondrial membrane; OS, overall survival; OSMR, oncostatin M receptor; pAKT, phosphorylated AKT; PARP1, poly(ADP)-ribose-polymerase 1; PDI, programmed cell death protein 1; PDGFRA, platelet derived growth factor receptor alpha; PDGFR, platelet derived growth factor receptor; PERK, protein kinase RNA like ER kinase; PFS, progression-free survival; P-gp, protein P-glycoprotein; PIAS2, Protein Inhibitor of Activated STAT-2; PI(3)K, phosphoinositide-3-kinase; PI3KCA, phosphoinositide-3-kinase, catalytic alpha subunit; PMS2, postmeiotic segregation increased 2; Pol-B, DNA polymerase B; POU3F2, POU domain, class 3, transcription factor 2; PKB, protein kinase B; PTCH1, Patched-1; PTEN, phosphatase and tensin homolog; PUMA, p53 upregulated modulator of apoptosis; RB1, retinoblastoma 1; RBBP6, retinoblastoma binding protein 6; RDC, ruthenium-derived compound; RNS, reactive nitrogen species; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; SALL2, spalt like transcription factor 2; SDF1, stroma cell derived factor 1; sFRP4, secreted frizzled-related protein 4; SGLT, sodium/glucose cotransporter; SHH, sonic hedgehog; shRNA, small hairpin RNA; SKIs, sphingosine kinase inhibitors; SNAI, snail family transcriptional repressor; SOX2, sex determining region-Y-box-2; SQSTM1/p62, sequetosome1/ubiquitin binding protein-62; SSBs, single strand breaks; SSBR, single strand break repair; STAT3, signal transducer and activator of transcription 3; TAK1, transforming growth factor beta-activated kinase 1; TCAs, tricyclic antidepressants; TCGA, The Cancer Genome Atlas; TERT, telomerase reverse transcriptase; TFs, transcription factors; TGF, transforming growth factor; TME, tumor microenvironment; TMZ, temozolomide; TNF, tumor necrosis factor; Top1, topoisomerase 1; TP53, tumor protein 53; TRAIL, TNF-related apoptosis inducing ligand; TRADD, TNF receptor associated death domain; TRPV2, transient receptor potential vanilloid-2; TTF, Time to treatment failure; TWIST, twist related protein; UBD, Ub-binding domain; ULK1, unc-51 like autophagy activating kinase 1; UPR, unfolded protein response; VEGF, vascular endothelial growth factor; WHO, World Health Organization; Wnt, wingless-type MMTV integration site family member; XBP1, X-box binding protein 1; YKL40, tyrosine (Y), lysine (K), leucine (L) 40 protein

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