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Glioma progression through the prism of heat shock protein mediated extracellular matrix remodeling and epithelial to mesenchymal transition

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ABSTRACT

Glial tumor is one of the intrinsic brain tumors with high migratory and infiltrative potential. This essentially contributes to the overall poor prognosis by circumvention of conventional treatment regimen in glioma. The underlying mechanism in gliomagenesis is bestowed by two processes- Extracellular matrix (ECM) Remodeling and Epithelial to mesenchymal transition (EMT). Heat Shock Family of proteins (HSPs), commonly known as "molecular chaperons" are documented to be upregulated in glioma. A positive correlation also exists between elevated expression of HSPs and invasive capacity of glial tumor. HSPs overexpression leads to mutational changes in glioma, which ultimately drive cells towards EMT, ECM modification, malignancy and invasion. Differential expression of HSPs – a factor providing cytoprotection to glioma cells, also contributes towards its radioresistance /chemoresistance. Various evidences also display upregulation of EMT and ECM markers by various heat shock inducing proteins e.g. HSF-1. The aim of this review is to study in detail the role of HSPs in EMT and ECM leading to radioresistance/chemoresistance of glioma cells. The existing treatment regimen for glioma could be enhanced by targeting HSPs through immunotherapy, miRNA and exosome mediated strategies. This could be envisaged by better understanding of molecular mechanisms underlying glial tumorigenesis in relation to EMT and ECM remodeling under HSPs influence. Our review might showcase fresh potential for the development of next generation therapeutics for effective glioma management.

1. Introduction

Glioma is one of the most intrinsic intracranial malignant tumors in human. The propensity for proliferation and invasion by glioma cells is one of the major pathologic hallmarks contributing towards failure of conventional therapeutic regimen (surgery/radiation/chemotherapy). The glial neoplastic cells with diffusive potential invade throughout the brain, through the unique neurological ambience. The biological correlation between glioma cells and prevailing neural environment appeals for a cohesive approach involving glioma's neurobiology and tumor biology, to hasten the progress in glioma management. Some of the key concerns such as determinants of molecular events initiating glioma, progression from low grade to high grade, lineage of differentiation and origin of tumors cells could be addressed by unraveling the neurobiology of the disease. The most fundamental biological processes in gliomagenesis are extracellular matrix (ECM) remodeling and epithelial–mesenchymal transition (EMT). The tumor cell growth and invasion is linked to ECM remodeling related proteolysis. EMT is an essential mechanism of glioma for transformation to infiltrating tumors from local tumors. Physiologically, basement membrane (BM) separates epithelial cells from the ECM preventing their interaction with the microenvironment. The destabilized BM activates contact between epithelial cells and various signaling ECM proteins. The expression of mesenchymal cytoskeletal proteins and deposition of ECM proteins promote migratory potential of glioma cells by activating integrins and their signaling pathways. They potentiate invasiveness and migratory potential of glioma cells leading to overall poor prognosis by circumvention of prevailing treatment regimen and therapeutic resistance [1,2].

In due course of progression in terms of attaining malignancy, the patients undergo various therapeutic management. This leads to generation of surviving cells of varied phenotypic characters with resistance to radiation or chemo therapy. Poor prognosis and therapeutic resistance are closely associated with elevated expression of heat shock proteins (HSPs) in glioma. The HSP members promote tumor growth by stimulating cell proliferation and inhibiting death pathways.

HSPs exhibit chaperone activity for many proteins including matrix degrading enzymes involved in ECM degradation. They orchestrate multiple components of ECM remodeling system indicating a positive correlation between high expression of HSPs and invasive or metastatic

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capacity of glioma cells. HSPs even play an essential extracellular role in the invasive phase of metastasis through its binding to MMPs. The molecular chaperone HSPs role in driving EMT in cancer at molecular level has been also reported. Upregulation in HSP expression is exhibited in both stages of gliomagenesis and acquisition of chemo or radio resistant phenotypes [3]. Hence, HSPs are potential targets providing an effective clinical strategy in the field of rational anti-glioma drug development.

2. Overview on gliomagenesis

Glioma, the tumor of glial cells accounts for 30% of brain cancer. On the basis of histopathology, protein signatures and clinical features, glioma is classified into four different grades by WHO. Pediatric glioma majorly comprises of low grade astrocytoma, whereas in adults, high grade and diffuse glioma are more commonly found. The specific location of the glial tumors in the brain and its size play an essential role in deciding the apt treatment regimen. The different molecular transformations influencing glial tumorigenesis as discussed in the review paper by Rajesh et al., are TP53, PTEN, CDKN2A, EGFR, TSC, histone, IDH, FGFR-TACC fusion and other mutations. Adult glioma have higher mutational burden of histone, EGFR, PTEN, ACVR1, FGFR1 and BRAF-V600E genes, whereas in pediatric glioma, the mutated genes are TP53, NF1, NTRK, PDGFRA, EGFR, CDK4, CDK6, cyclin D1, histone and K27M. The major challenges coming across the path of glioma stratification are – tumor heterogeneity, recurrence, infiltrative nature, surgical abscission complications (acute morbidity, need for ventriculoperitoneal shunting), developing therapeutic resistance (chemo/radio), bypassing blood brain barrier, lack of glioma models, etc. During gliomagenesis, a number of cells escape from the tumor mass, move out of the original clump of mutant cells, and set out invading nearby tissues followed by distant metastasis. These distant settlements of cancer cells are responsible for reduced survival rates and prognosis of patients [4]. Inquisition of the mechanistic approach of this distant settlements or metastasis is bestowed by two processes- Extracellular matrix (ECM) Remodeling and Epithelial to mesenchymal transition (EMT). The different ECM and EMT markers upregulated or downregulated during glioma progression has been listed in Table 1.

2.1. Extracellular matrix (ECM) remodeling in glioma progression

The major challenge in glioma treatment is the migratory potential of glioma cells breaching into the blood–brain barrier (BBB) protected areas of brain. Hence, unraveling the migration aspect in glioma biology has always been of great research importance in glioma field. The major players contributing towards migratory potential of cells are ECM degradation through matrix metalloproteases (MMPs), intracellular cytoskeletal rearrangements, and stimuli to chemo attractants. But, so far, no clear demarcation has been identified in migratory biology of glial tumor cells and normal glial cells/adult neural stem and glial progenitor cells. Thus we are left with very limited options for selectively targeting the migratory hallmark of glioma without affecting normal glial cells/stem cells. Such therapeutic targeting of MMPs degrading ECM proteins fail to differentiate during the course of disease [1].

The four distinct processes required for glioma cell invasion are -

(i) Destabilization and disorganization of cadherin-mediated junctions leading to detachment of cells from primary tumor mass, downregulation of neural cell adhesion molecule and metalloproteinase ADAM mediated CD44 cleavage (anchorage between primary mass and ECM)
(ii) *αvβ3* integrins mediated ECM adhesion by binding to fibronectin
(iii) MMP-2/9 mediated ECM degradation
(iv) Myosin mediated cell motility and intracellular contractility [8].

2.2. Epithelial to mesenchymal transition (EMT) in glioma progression

EMT is a significant proceeding in the transition to infiltrating and metastasizing tumors from local tumors. The high infiltrative and migratory potential of glioma cells contribute towards it overall poor prognosis by evasion of effective conventional treatment strategies. EMT also leads to resistance of glioma cells towards various therapeutic strategies [6]. EMT is characterized by the loss of E-cadherin and the elevation in N-cadherin expression. This cadherin switch is a pivotal step in EMT allowing cells to initiate metastasis. But in healthy brain tissue, astrocytes, oligodendrocytes and even in diseased GBM brain; E-cadherin is not expressed. During local invasion glioma cells undergo different form of EMT excluding the canonical cadherin switch and using single transcription factor Twist for initiating EMT [7]. In GBM, the infiltration into normal brain parenchyma occurs along the fibrous tracts lining the outer walls of the brain and myelinated white matter tracts [5].

EMT triggers CSCs for metastasizing from original microenvironments. The MMPs majorly aid in degrading the basement membrane along with ECM. During EMT, MMPs secreted by glioma cells and stromal cells facilitate ECM remodeling, invasiveness by ECM degradation, promoting migration by release of growth factors embedded within the ECM for activation of signal transduction cascades. The levels of MMPs are largely correlated with histological grading of glioma. In GBM both MMP-2/9 are implicated in proliferation and migration by activating TGF-α and TGF-β and the transcription factor Twist upregulates MMP-2 gene's expression [5,7].

Table 1
The different ECM and EMT markers upregulated/downregulated during glioma progression.

	Glioma		Radioresistance		Chemoresistance		Ref.
	Up	Down	Up	Down	Up	Down	
ECM Markers	Hyaluronic Acid Proteoglycan Vitronectin Fibronectin Laminin Collagen IV MMPs		MMPs Vitronectin Integrins		MMPs Vitronectin Integrins		[5]
EMT Markers	Twist1 SNAI-1 SLUG TGF-β SMAD	E-cadherin Claudins Occludins Laminin-1	Vimentin SNAI-1 Sox-2 Oct-4 β-catenin	E- cadherin	Vimentin SNAI-1 Sox-2 Oct-4 β-catenin	E-cadherin	[6,7]