ABSTRACT

Glioblastoma (GBM), a faction of tumors arising from neural stem cells, glial progenitors, astrocytes and progeny cells of mutations forms the most infiltrative genre of malignant brain tumors. It's extremely poor prognosis with current management and lack of potential chemotherapeutic agents demands the rapid buildout of potential therapeutic targets. Two processes that are instrumental in GBM advancement are the EMT-like process and ECM remodeling which enhances its migratory and infiltrative potential. We have hypothesized a mechanistic model of GBM stating that the HSPs while interacting with MMPs have a synergistic effect on the promotion of GBM. HSP27 was found to be interacting with both MMP-2 and MMP-9, and this association was found to be of prime significance in GBM progression. The analysis of precise interaction site of HSP27 (amino acid stretch AA 29-40) with MMP-2 and MMP-9, opens up avenues for potential drug design for GBM. It has been also observed that ECM remodeling and EMT-like characteristics are involved in the acquisition of radiation and temozolomide (TMZ) resistance. The HSPs are one of the major protein signatures and biomarkers for radio/TMZ resistant GBM. For the first time we identified that Fli-1 orchestrates ECM remodeling and EMT-like characteristics in GBM via transcriptional regulation of HSP27. Fli-1 modulated downstream pathways of ECM remodeling and EMT-like characteristics promoting GBM transformation and therapeutic resistance. We have also identified that lumefantrine, an anti-malarial drug; can inhibit the transcriptional activities of Fli-1. The drug showed significant selective cytotoxicity towards GBM and was also able to reverse the radio and TMZ resistance in GBM. Thus it can be assumed that the drug could be easily repurposed for management of GBM. Additionally, oxidative stress along with ECM remodeling has also been found to be involved in gaining temozolomide (TMZ) resistance. We have established NFE2L2, an important member of oxidative stress regulation elevated in TMZ resistant cells, to be playing a transcriptional regulatory role on MMP-2, an ECM remodeling marker. This link led us to further explore targeted molecules to inhibit NFE2L2, thus affecting MMP-2, an important member promoting TMZ-resistance. Thus, diosgenin was proposed as a novel NFE2L2 inhibitor acting as an alternative strategy to prevent the high dose administration of TMZ. Combinatorial therapy of diosgenin and TMZ significantly reduced the dosage regimen of TMZ and also showed effectivity in hitherto TMZ resistant GBM cells. Thus, our study proposes a multi-dimensional approach towards glioblastoma management by analysis of the molecular regulation of its migration and infiltration and potential therapies against the same.