Glioblastoma Stem Cells and Withaferin A, A Review

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Introduction

Glioblastoma multiforme is characterized by tumor cell heterogeneity, and by recurrent invasive tumors following conventional radiation, cytotoxic drugs, and limited ablative surgery [1-5]. The tumor originates from a stem cell population which exhibits properties of self-renewal and multi-lineage differentiation followed by clonal evolution, hierarchical stem cell development and bidirectional inter-conversion with non-stem cells [6]. These observations indicate that it is necessary to eradicate glioblastoma stem cells in order to abrogate the enhanced risk of tumor recurrence following conventional chemotherapy surgery, and radiation. The therapeutic focus should initially consist of applying pleiotropic medicinal (supplements, drugs) directed to the multiple molecular pathways promoting tumor stem cell genesis. Based on published pre-clinical research [7], pleiotropic compounds such as withaferin A, [8] and curcumin can be considered appropriate candidate agents [9]. There are several published withaferin A inhibitory interactions with critical molecular pathways in glioblastoma stem cells promoting tumor development (Table 1), There are also pre-clinical studies with withaferin A prohibiting tumor development in other tumors, but unexplored in glioblastoma stem cells (Tables 2 & 3).

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Proteins</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedgehog Signaling</td>
<td>PTCH1, Gli1 and Gli2 [10]</td>
<td>Withaferin A showed strong inhibition of Hh/GLI1-mediated transcriptional activity with IC50 values of 0.5 mM [11]</td>
</tr>
<tr>
<td>Notch signaling</td>
<td>Notch-1, Akt/NF-κB/Bcl-2 [12-15]</td>
<td>Withaferin A inhibits Notch-1 signaling and down-regulates pro-survival pathways, such as Akt/NF-κB/Bcl-2 [16,17]</td>
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<td>GFAP (Glial fibrillary acidic protein) [18,19]</td>
<td>Witherfaerin A decreases the expression of GFAP [20]</td>
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<tr>
<td>VEGF (Vascular endothelial growth factor) [21]</td>
<td>Withaferin A binding with VEGF has low binding energy and is a potent anti-VEGF agent [22]</td>
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<tr>
<td>BNDF (Brain-derived neurotrophic factor) [21]</td>
<td>Withaferin A applied to a hippocampal cell culture model of nutrient deprivation stress results in activation of the pro-survival Akt/PI-3K and MAPK cascades, CREB phosphorylation, BDNF production, and neuronal survival [23]</td>
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Table 2: Published Withaferin A interactions with tumor stem cells other than glioblastoma stem cells.

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<thead>
<tr>
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<tbody>
<tr>
<td>Wnt/β-catenin signaling</td>
<td>Wnt [26]</td>
<td>Withaferin A inhibits Wnt/β-catenin signaling through degradation of transcription factor (TCF)/lymphoid enhancer-binding factor (LEF) family members in medulloblastoma [27]</td>
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<td></td>
<td>CD133 (a pentaspan membrane glycoprotein) [28]</td>
<td>CD133+ ovarian stem cells are inhibited by withaferin A [29]</td>
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<td></td>
<td>BMI1) B-cell-specific Moloney murine leukemia virus insertion region-1 [30]</td>
<td>Withaferin-A treatment reduced the level of Bmi protein in malignant mammary stem cells [31]</td>
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<td>IL-8 [34]</td>
<td>Withaferin A inhibits IL-8 in an in vitro model of cystic fibrosis-related inflammation [35]</td>
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<td></td>
<td>TP53 [36]</td>
<td>TP53 is induced by Withaferin A in cervical cancer [37]</td>
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Table 3: Unstudied interactions of Withaferin A and factors in glioblastoma stem cells.

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<tbody>
<tr>
<td>Wnt/β-catenin signaling</td>
<td>PLAGL2 (Pleiomorphic adenoma gene like 2) [38]</td>
<td>Unstudied</td>
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<tr>
<td></td>
<td>BMPs (Bone morphogenic proteins) [39-42]</td>
<td></td>
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<td></td>
<td>Hypoxia signal transduction pathways [43]</td>
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<td></td>
<td>NF1 (neurofibromatosis Type 1) [44]</td>
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<td></td>
<td>OLG2 (Oligodendrocyte lineage transcription factor) [45]</td>
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<td>PDGF (Platelet-derived growth factor) [46]</td>
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Conclusion

Gliomagenesis and tumor stem cell heterogeneity are promoted by genetic alterations (driver mutations) and multiple factors in the surrounding tumor microenvironment [47,48]. An additional mechanism for post-therapeutic reestablishment of an invasive and chemo/ radiation resistance population of differentiated glioblastoma cancer cells into cancer stem-like cells expressing markers associated with pluripotency and stemness such as CD133, SOX2, Oct4, and Nestin has been published [48]. These observations emphasize the importance of preclinical research studies with pleiotropic compounds interacting in a specific manner with tumor stem cells and avoiding interacting with normal stem cells. In the clinical setting, Withaferin A alone, or in combination with other pleiotropic approved drugs or supplements as initial therapy following diagnosis of glioblastoma multiforme [49-53] may prohibit or delay tumor recurrence assuming these agents abrogate the effects of driver mutations, and micro-environmental factors.

References


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