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Wingless (WNT) antagonist, sFRP4 sensitizes glioblastoma stem cells to chemotherapeutic drug, doxorubicin by the apoptotic and antioxidant pathways

Prathyusha Pavanram
National Center for Biological Sciences, India

The treatment of glioblastomamultiforme (GBM) is a challenge worldwide in the field of oncology. Despite the development of advanced surgical interventions, radiation therapies and the use of multiple anti-cancer drugs, a cure for GBM remains unclear. The low efficacy of current treatments is explained by the cancer stem cell hypothesis that verifies, solid tumours are maintained by a small population of cancer cells with stem cell properties and chemo-resistant properties. Hence, the key lies in improving the effectiveness of chemotherapy by targeting cancer stem cells (CSCs). This study aims at targeting glioblastoma CSCs obtained from the U138MG glioblastoma cell line, using an inhibitor of WNT pathway namely secreted frizzled related protein 4 (sFRP4).

Materials and Methods: Our methodology included the establishment of a successful protocol for U138MG sphere enrichment and characterization. Also standardisation of optimal concentrations of sFRP4 and Doxorubicin when used in combination for treatment purpose was done. After combination treatment, JC1 Assay, Colony Forming Unit assay, Secondary sphere formation assay, Differentiation assay, were done along with checking the anti-oxidant gene expression levels.

Results: Efficient U138MG sphere enrichment was seen when cells were grown on low adherent dishes using serum free medium supplemented with B27. The enriched spheres being CSCs showed positivity for markers like CD133, Nestin and p-glycoprotein. 125pg/ml concentration of sFRP4 and 50ng/ml concentration of Doxorubicin were found most suitable for usage as combination treatment in this study. The combination treatments on CSCs showed an increase in cellular apoptosis and differentiation ability. It also showed decrease in anti-oxidant gene expression and self-renewal ability.

Conclusion: This study demonstrates that the drug refractory CSCs are made more responsive to drugs such as doxorubicin upon treatment with sFRP4. This treatment also showed decreased stemness property of CSCs. Thus, this study opens up novel routes for better combinatorial cancer treatment.

prathyusha89@gmail.com