Glioblastoma stem cell

The modest benefit of conventional therapies is due to the presence of glioblastoma stem cells (GSCs) that cause tumor relapse and chemoresistance and, therefore, that play a key role in GBM aggressiveness and recurrence. So far, strategies to identify and target GSCs have been unsuccessful. Thus, the development of an approach for GSC detection and targeting would be fundamental for improving the survival of GBM patients. Here, using the cell-systematic evolution of ligand by exponential (SELEX) methodology on human primary GSCs, we generated and characterized RNA aptamers that selectively bind GSCs versus undifferentiated GBM cells. We found that the shortened version of the aptamer 40L, which we have called A40s, costained with CD133-labeled cells in human GBM tissue, suggestive of an ability to specifically recognize GSCs in fixed human tissues. Of note, both 40L and A40s were rapidly internalized by cells, allowing for the delivery of the microRNA miR-34c and the anti-microRNA anti-miR-10b, demonstrating that these aptamers can serve as selective vehicles for therapeutics. In conclusion, the aptamers 40L and A40s can selectively target GSCs. Given the crucial role of GSCs in GBM recurrence and therapy resistance, these aptamers represent innovative drug delivery candidates with great potential in the treatment of GBM [1)].

Experimental evidences suggest that the presence of therapy-resistant glioblastoma stem cells (GSCs) could explain recurrent glioblastoma and metastasis. Some scientists, believe that GSCs are the driving force behind GBM relapses, whereas others however question the existence of GSCs. Evidence has accumulated indicating that non-tumorigenic cancer cells with high heterogeneity, could undergo reprogramming and become GSCs. Hence, targeting GSCs as the “root cells” initiating malignancy has been proposed to eradicate this devastating disease. Most standard treatments fail to completely eradicate GSCs, which can then cause the recurrence of the disease. To effectively target GSCs, a comprehensive understanding of the biology of GSCs as well as the mechanisms by which these cells survive during treatment and develop into a new tumor, is urgently needed [2)].

Ion channel expression may be perturbed in this population. However, little is known about the expression and functional relevance of ion channels that may contribute to GSC malignancy.

Using RNA sequencing, Pollak et al. assessed the enrichment of ion channels in GSC isolates and non-tumor neural cell types.

They identified a unique set of GSC-enriched ion channels using differential expression analysis that is also associated with distinct gene mutation signatures. In support of potential clinical relevance, expression of selected GSC-enriched ion channels evaluated in human glioblastoma databases of The Cancer Genome Atlas and Ivy Glioblastoma Atlas Project correlated with patient survival times. Finally, genetic knockdown as well as pharmacological inhibition of individual or classes of GSC-enriched ion channels constrained growth of GSCs compared to normal neural stem cells. This first-in-kind global examination characterizes ion channels enriched in GSCs and explores their potential clinical relevance to glioblastoma molecular subtypes, gene mutations, survival outcomes, regional tumor expression, and experimental responses to loss-of-function. Together, the data support the potential biological and therapeutic impact of ion channels on GSC malignancy and provide strong rationale for further examination of their mechanistic and therapeutic importance [3)].

Glioblastoma stem cell (GSC)s can promote neoangiogenesis, modulate endothelial cell functions and may even transdifferentiate into endothelial cells. Accordingly, targeting tumor vasculature seems a promising issue despite incomplete and transient results obtained from anti-vascular endothelial growth factor therapeutic trials.

Findings of novel GSC-secreted molecules with pro-angiogenic properties (Semaphorin 3A, hepatoma derived growth factor) open the path to the design of a concerted attack of glioblastoma vasculature that could overcome the development of resistance to single-targeted therapies while keeping away the toxicity of the treatments [4].

Within Glioblastoma multiforme, stem-like cells, namely glioblastoma stem cells (GSCs), have the ability to self-renew, differentiate into distinct lineages within the tumor and initiate tumor xenografts in immunocompromised animal models. More importantly, GSCs utilize cell-autonomous and tumor microenvironment-mediated mechanisms to overcome current therapeutic approaches. They are, therefore, very important therapeutic targets. Although the functional criteria defining GSCs are well defined, their molecular characteristics, the mechanisms whereby they establish the cellular hierarchy within tumors, and their contribution to tumor heterogeneity are not well understood. A better characterization of GSCs is crucial for designing effective GSC-targeted therapies [5].

Results suggest that undifferentiated GSCs are oxygen dependent, and that limited differentiation induces relative hypoxia tolerance. Hypoxia tolerance may be a factor involved in high-grade malignancy. This warrants a careful approach to differentiation as a glioblastoma treatment strategy [6].

Quantitative RT-PCR analysis showed that monocarboxylate transporter1 (MCT1) were upregulated in GSCs, and inhibition of MCT1 decreased the viability of GSCs compared with that of non-GSCs. The findings indicate that MCT1 is involved in the maintenance of GSCs and is a promising therapeutic target for glioblastoma [7].

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