S100A4, a key factor in glioblastoma biology

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Glioblastoma: a heterogeneous glioma entity

Glioblastoma (GBM) is the highest grade of glioma and the most common malignant primary brain tumor in adults. The present World Health Organization classification distinguishes IDH-wildtype and IDH-mutant GBMs, which correspond closely to so-called primary (*de novo*) and secondary GBMs, respectively (1). While being considered as a single histological entity, primary GBM is heterogeneous with considerable variability in terms of biological behavior, response to treatment and clinical outcome. It is associated with poor prognosis and a median overall survival between 15 and 21 months only, depending of treatment (2). GBM was recently classified into four molecular subgroups, namely neural, proneural, classical and mesenchymal, characterized by different gene expression signatures. These subgroups are associated with different prognoses and/or therapy responses, with the worst prognosis observed for the mesenchymal (MES) subgroup. Transitions from the proneural and classical subtypes to the MES one were often observed at recurrence and may be due to standard treatments involving surgery, radio- and chemotherapy (3,4). This transition can be linked to the epithelial-to-mesenchymal transition (EMT)-like process occurring in GBM and recently reviewed by Iser *et al.* (5).

EMT and stemness in GBM

EMT is a developmental program that is normally employed during embryogenesis and for the healing of epithelial tissues, but is also identified in cancers. EMT refers to a transient process where flat, sessile, mutually adherent epithelioid cells take on a rounded, non-adherent, motile mesenchymal shape and behavior. In cancer, this complex process allows tumor cells to acquire invasive properties as well as the tumor microenvironment to be modified for easing cancer progression and metastasis (6-8). In cancer EMT has been also associated with acquisition of stemness, in general (7) and for GBM in particular (9,10). Glioma stem cells (GSCs) are a subset of tumor cells that possess self-renewal and multi-lineage differentiation properties similar to somatic stem cells. They are highly interactive with their microenvironments and contribute to tumor initiation and also therapy resistance. In order to treat GBM more efficiently, a better understanding of GSC biology is necessary (11).

S100A4: a key actor

In their recent paper, Chow *et al.* (12) evidence that S100A4, a member of calcium-binding proteins, plays key roles in the processes of stemness and EMT in GBM. Previous studies already provided data on S100A4 involvement in glioma biology. S100A4 was shown as promoting glioma cell migration *in vitro* and impacting different regulators of the actin cytoskeleton (13). S100A4 expression was evidenced as higher in GBM, compared with low-grade astrocytic tumors,

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suggesting its involvement in glioma progression (14,15). Liang *et al.* (16) confirmed that glioma progression with mesenchymal characteristics was partly mediated by S100A4, the expression of which is increased by neutrophil infiltration. Finally, the involvement of S100A4 in EMT is not new (17) but requires specific data for GBM. Responding to this need, Chow *et al.*'s study (12) provides strong clarifications about the potential roles played by S100A4 in the GBM context. More particularly, Chow *et al.* show that:

(I)   S100A4 is strongly associated with the mesenchymal phenotype in human GBMs and might play a significant role in proneural-to-mesenchymal transition;

(II) S100A4 expressing cells are enriched with long-term self-renewing ability and tumorigenic cells *in vivo* and *in vitro*;

(III) S100A4-positive cells preferentially localize to the perivascular region *in vivo*;

(IV) Cells overexpressing S100A4 are quiescent or slow cycling;

(V)   Selective ablation of S100A4-expressing tumor cells is sufficient to block tumor growth *in vivo*;

(VI) S100A4 is an upstream regulator of EMT actors.

The authors concluded that S100A4 is a novel marker of GSCs, a regulator of GSC proliferation, survival, self-renewal and tumor growth as well as an upstream regulator of the mesenchymal transition in GBM.

New perspectives for GBM treatment

The new data provided by Chow *et al.* open new perspectives for GBM treatment. In the field of cancer research, the concept of precision medicine—namely treatment strategies that take individual variability into account—relies on the development of valid biomarkers highlighting key aberrant pathways potentially targetable with molecular targeted therapies (18). The current GBM treatment standards consist in achieving maximal surgical resection followed by radiotherapy with concomitant and adjuvant chemotherapies (19). Despite these aggressive therapeutic strategies, the majority of patients suffer recurrence due to molecular heterogeneity of GBM. Consequently, a number of potential diagnostic, prognostic, and predictive biomarkers have been investigated (20). Beyond IDH1 mutations, 1p19q deletion, MGMT promoter methylation and EGFR amplification, the accumulated genetic characterization of GBMs has failed so far to impact clinical practice. GSCs, this subpopulation

of cells that exhibit enhanced self-renewal capacity and compromised differentiation within GBM, potentially contribute to this failure. Indeed, increasing evidence shows that GSCs play key roles in tumor recurrence and therapy resistance (21). These observations thus designate GSCs as relevant targets for GBM therapy. Several markers for GSCs have been proposed and studied (CD133, CD15, CD44…). However, these markers must be considered with caution since each of them lacks of specificity: each may be expressed in various cell types (other than GSC) and/or does not identify all GSC subgroups (11,22).

In their paper, Chow *et al.* propose S100A4 as a novel biomarker of GSCs. S100A4-positive cells in gliomas have tumor-initiating, sphere-forming and long-term self-renewing abilities, i.e., all features of GSCs. They also report that selective ablation of *S100A4* blocks tumor growth. These results show the interest to develop anti-S100A4 therapy for direct impact on GBM aggressiveness. S100A4 is expressed in several types of cancer cells and its overexpression has been associated with poor survival of cancer patients, as recently reviewed by Fei *et al.* (23). Several strategies have been therefore already evaluated in preclinical studies to target S100A4 such as RNAi-based knockdown, small molecule inhibitors, indirect inhibition via Wnt/β-catenin signaling suppression, neutralizing S100A4-specific antibodies, etc. (23). Validation of these putative anti-S100A4 therapies in clinical trials is now needed. Directly targeting GSCs presents a promising opportunity to eliminate the likely source of gliomas and the nest of their recurrence with the hope to improve patient outcomes and survival. However, as GSCs are characterized by different molecular programs, an anti-GSC therapy focusing on a single target will probably not show a sufficiently broad activity; instead, GSCs will demand multitargeted approaches.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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