Therapeutic strategies to target glioblastoma multiforme: the cancer stem cells model

The treatment and cure of Glioblastoma multiforme (GBM) still remains an unresolved issue. GBM is the most aggressive and recurrent brain derived cancer, with a median patient survival of 14 months; its infiltrative and aggressive nature renders conventional treatments, such as resection, radiation, and chemotherapy, relatively ineffective. GBM progression and recurrence strongly correlate with the existence of cancer stem cells (CSC), a small population of tumor initiating cells that have an enhanced resistance to radio- and chemotherapy in many cancer types. Therefore, targeting CSC by inhibiting relative pathways and factors is crucial for complete tumor eradication and anti-CSC drugs can improve the therapeutic efficacy of GBM treatment (1,2). We recently reported the anti-tumor effects of acetylsalicylic acid (ASA) in GBM derived CSC. The results of this study suggest that ASA might be useful as an adjuvant therapy in the treatment of GBM patients (1). GBM is characterized by a large number of genetic alterations associated with specific GBM phenotypes, and the overexpression and alterations of NOTCH1, EGFR and PDGFR, observed either in GBM and GBM derived CSC, ultimately might contribute to uncontrolled growth of the tumor. In the last years, the main goal of our research focused on the role played by these receptors and intracellular signals and conceiving the therapeutic strategies to eliminate GBM. Anti-EGFR and -PDGFR pharmacologic targeting decreased the survival and invasiveness of CSC (2). In addition, PDGFRα-directed shRNA significantly reduced STAT3-Tyr705, invasiveness, angiogenesis and epithelial-mesenchymal transition (3). The interference of NOTCH1 target HES1 affected cell growth, differentiation and invasiveness of CSC through modulation of multiple oncogenic signals (4). Clinical studies with small molecules targeting EGFR has proven largely disappointing, suggesting that a direct immune-mediated targeting of this marker could be more effective. For this reason, we have a collaboration ongoing with Dr. Giuseppe Sconocchia, (IFT-CNR), with expertise in tumor immunotherapy, to assess atypical CAR-T cell-based immunotherapy in combination with therapeutic monoclonal antibodies in GBM. Recently, we have another collaboration ongoing with Dr. Igea D'Agnano, (ITB-CNR, Milano), aimed at the identification of biomarkers by the proteomic and miRNA analyses on exosomes secreted by GBM derived CSC. The goal of this line of research aims to define a specific molecular signature of GBM, and to highlight the exosomes obtained from GBM associated CSC as potentially useful for diagnostic and prognostic purposes.

References:
(3) Cenciarelli C et al., *Oncotarget*. 2016. 7(33) 53047-63.

**Keywords:** Glioblastoma cancer stem cells, anti-cancer drugs, immunotherapy.

**Contacts:** carlo.cenciarelli@ift.cnr.it. **ORCID:** [https://orcid.org/0000-0001-7480-4608](https://orcid.org/0000-0001-7480-4608)