

New promises from targeting stromal-cancer cell crosstalk in glioblastoma

Glioblastoma (GB) is the most frequent primary brain tumor in adults. The prognosis of GB is poor: median survival time is less than one year since the diagnosis and patients usually die within two years. Standard therapy, including surgical resection, followed by concomitant radiotherapy and temozolomide therapy, could not avoid fatal relapses. One possible reason for such aggressive behavior consists in the capacity of GB cells to efficiently interact and infiltrate the surrounding normal tissue. Tumor microenvironment consists of a dynamic mixture of stromal cells and extracellular matrix (ECM), and plays a critical role during tumor initiation, angiogenesis, progression and metastasis. The carcinoma-associated fibroblasts (CAFs), an important component of the tumor stroma, are able to support, in different ways, the continuous growth of cancer cells. In fact, they participate in each step of angiogenesis and may be responsible for mediating resistance to chemotherapeutic, anti-angiogenesis drugs and other targeted therapies. Stromal cells, through cytokines secretion, can modulate the ECM remodeling, suppress immune responses and affect tumor growth and invasiveness. In the last decade, fibroblast-like cell population has been identified in several solid tumors and it was recently described in computer-guided stereotaxic biopsies from GB surrounding tissue. These cells express CAFs associated markers including fibroblast surface protein, alpha-smooth muscle actin (α -SMA), and β -PDGFR. The role of these cells in GB progression is largely unknown, but available data indicate that they actively crosstalk with cancer cells.

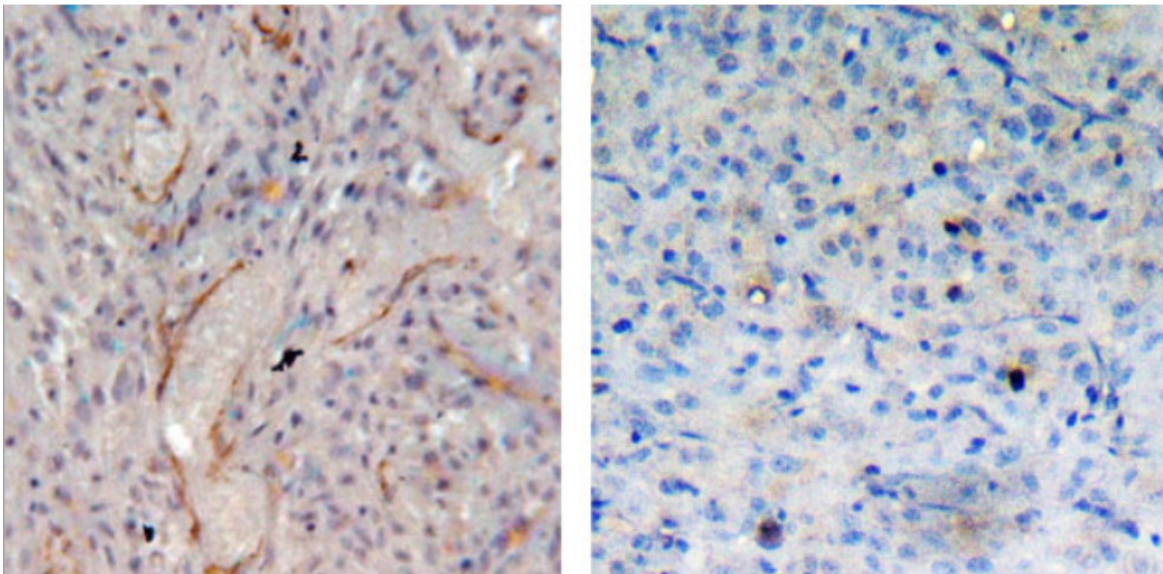


Fig. 1. Representative microscopy images of human glioblastoma tissue growing in mouse brain. On the left, tissue from untreated mouse, on the right tissue from mouse treated with SRC inhibitor. The brown staining indicates the presence of myofibroblasts and it is evident only in untreated mice.

A new therapeutic drug able to interfere with GB capacity to synergize with normal brain tissue could represent an effective strategy in ameliorating GB prognosis. We have tested the hypothesis that the

formation of CAF could be blocked by controlling the release of promoting factors from GB cells. The protein SRC, frequently overexpressed in many GB, could play a central role in determining this effect. For this reason the compound Si306, a pyrazolo[3,4-*d*]pyrimidine derivative, selected for its favorable activity against SRC, was tested in vitro and in vivo on GB cell lines. Si306 was able to interfere with myofibroblastic differentiation of normal fibroblasts induced by GB U-87 cells, inhibiting the release of tumor-associated growth factors. In vivo, the combination treatment with Si306 and radiotherapy (RT) was strongly active in reducing tumor growth with respect to control and single treatments. The histology revealed a significant difference in the stromal compartment of tumoral tissue derived from control or RT-treated samples with respect to Si306-treated samples, showing in the latter a reduced presence of ECM and CAF. Si306 efficiently reached the brain and significantly prolonged the survival of mice injected with U-87 cells.

Drugs that target SRC could represent an effective therapeutic strategy in GB able to block positive paracrine loop with stromal cells and the formation of a tumor-promoting microenvironment. This approach could result important in combination with conventional treatments in the effort to reduce tumor resistance to therapy.

Adriano Angelucci

Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università dell'Aquila, L'Aquila, Italy

Publication

[Suppression of SRC Signaling Is Effective in Reducing Synergy between Glioblastoma and Stromal Cells.](#)

Calgani A, Vignaroli G, Zamperini C, Coniglio F, Festuccia C, Di Cesare E, Gravina GL, Mattei C, Vitale F, Schenone S, Botta M, Angelucci A

Mol Cancer Ther. 2016 Jul