Abstract
The novel classification of gliomas incorporates the genetic status of Isocytrate Dehydrogenase 1/2 (IDH1/2) to the histological analysis. Mutant IDH1/2 gliomas have a much better clinical behavior than their wild-type counterparts. However, how these two groups of gliomas progress, in a microenvironment-dependent manner, is still a pending question. We have recently found that the expression of Tau, a microtubule stabilizer that has been classically associated with neurodegenerative diseases, depends on the status of IDH1/2, being epigenetically induced by the mutant isoforms of these metabolic enzymes. We have observed that Tau overexpression or microtubule stabilizers impair the mesenchymal transformation of glioma cells through the blockade of the EGFR-NFkB-TAZ axis. However, in the presence of EGFR mutations, there is a constitutive activation of this pathway, which is no longer sensitive to Tau overexpression. By inhibiting the phenotypic plasticity of EGFRamp/wt glioma cells, Tau protein inhibits angiogenesis, favors vascular normalization, and significantly decreases tumor burden. On the other hand, epithelial-to-mesenchymally (EMT) transformed EGFR-mutant cells, have the capacity to migrate towards endothelial cells, acting as bona-fide pericytes. By doing so they induce neo-vasculogenesis, stabilize the tumor vessels and favor aggressive glioma growth, in a Tau independent manner.
Our findings indicate that the main genomic alterations of gliomas, which together account for 80% of the samples, control the vascular landscape by modifying the capacity EMT capacity of tumor cells and the appearance of glioma-derived-pericytes. We propose a novel stratification of gliomas based on the different vascular alterations, which could significantly improve the diagnostic and predictive radiological parameters. Moreover, it could serve to design tailor-made therapies for each subgroup of tumors.