Mesenchymal glioblastoma

Among the identified transcriptional subtypes, the mesenchymal subtype has been found associated with more aggressive, invasive, angiogenic, hypoxic, necrotic, inflammatory, and multitherapy-resistant features than other transcriptional subtypes. Accordingly, mesenchymal Glioblastoma patients were found to exhibit worse prognosis than other subtypes when patients with high transcriptional heterogeneity were excluded. Furthermore, identification of the master mesenchymal regulators and their downstream signaling pathways has not only increased our understanding of the complex regulatory transcriptional networks of mesenchymal Glioblastoma, but also has generated a list of potent inhibitors for clinical trials. Importantly, the mesenchymal transition of Glioblastoma has been found to be tightly associated with treatment-induced phenotypic changes in recurrence. Together, these findings indicate that elucidating the governing and plastic transcriptomic natures of mesenchymal Glioblastoma is critical in order to develop novel and selective therapeutic strategies that can improve both patient care and clinical outcomes [1)].

Although the mesenchymal signature in malignant glioma may seem at odds with the common idea of the ectodermal origin of neural-glial lineages, the presence of the mesenchymal signature in glioma is supported by several studies suggesting that it can result from: (i) intrinsic expression of tumour cells affected with accumulated genetic mutations and cell of origin; (ii) tumour micro-environments with recruited macrophages or microglia, mesenchymal stem cells or pericytes, and other progenitors; (iii) resistance to tumour treatment, including radiotherapy, antiangiogenic therapy and possibly chemotherapy. Genetic abnormalities, mainly NF1 mutations, together with NF-κB transcriptional programs, are the main driver of acquiring mesenchymal-signature. This signature is far from being simply tissue artefacts, as it has been identified in single cell glioma, circulating tumour cells, and glioma stem cells that are released from the tumour micro-environment. All these together suggest that the mesenchymal signature in glioblastoma multiforme is induced and sustained via cell intrinsic mechanisms and tumour micro-environment factors. Although patients with the mesenchymal subtype tend to have poorer prognosis, they may have favourable response to immunotherapy and intensive radio- and chemotherapy [2)].

Marques et al. identified the AP-1 transcription factor FOSL1 as a key regulator of the mesenchymal glioblastoma subtype.

They provided a mechanistic basis to the role of the neurofibromatosis type 1 gene (NF1), a negative regulator of the RAS/MAPK pathway, in Glioblastoma mesenchymal transformation through the modulation of FOSL1 expression. Depletion of FOSL1 in NF1-mutant human BTSCs and Kras-mutant mouse neural stem cells results in loss of the mesenchymal gene signature and reduction in stem cell properties and in vivo tumorigenic potential. This data demonstrates that FOSL1 controls Glioblastoma plasticity and aggressiveness in response to NF1 alterations [3)].

The Mesenchymal glioblastoma subgroup contains the most frequent number of mutations in the NF1 tumor suppressor gene (37 percent). Frequent mutations in the PTEN and TP53 tumor suppressor genes also occurred in the group. Patients in the Mesenchymal group had significant increases in

survival after aggressive treatment, unlike those in the Proneural, and to an extent, in the Neural subgroups.

Signal transducer and activator of transcription 3 (STAT3), a critical transcriptional activator in tumorigenesis, is persistently phosphorylated and associated with an unfavorable prognosis in glioblastoma multiforme (Glioblastoma). Although a set of specific targets has been identified, there have been no systematic analyses of STAT3 signaling based on Glioblastoma subtype.

A study compared STAT3-associated messenger RNA, protein, and microRNA expression profiles across different subtypes of Glioblastoma.

The analyses revealed a prominent role for STAT3 in the mesenchymal but not in other Glioblastoma subtypes, which can be reliably used to classify patients with mesenchymal Glioblastoma into 2 groups according to phosphorylated STAT3 expression level. Differentially expressed genes suggest an association between Notch signaling pathway and STAT3 signaling in the mesenchymal subtype. Their association was validated in the U87 cell, a malignant glioma cell line annotated as mesenchymal subtype. Specific associated proteins and microRNAs further profile the STAT3 signaling among Glioblastoma subtypes.

These findings suggest a prominent role for STAT3 signaling in mesenchymal glioblastoma (Glioblastoma) and highlight the importance of identifying signaling pathways that contribute to specific cancer subtypes [4].

1)
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