Proneural glioblastoma

Proneural glioblastoma is common in young adults, corresponds to the secondary glioblastoma subtype, has neuronal differentiation, and is associated with better outcome. Is characterized by IDH/TP53 mutations/positivity for the glioma-CpG island methylator phenotype (G-CIMP) and normal EGFR/PTEN/Notch signaling. The G-CIMP phenotype, like IDH mutation, appears to be a general feature of lower grade gliomas, and practically speaking, provides a molecular definition of secondary glioblastoma [1)]

GPR56 is enriched in proneural glioblastoma and classical GBMs and is lost during their transition toward a mesenchymal subtype. GPR56 loss of function promotes mesenchymal differentiation and radioresistance of glioma initiating cells both in vitro and in vivo. Accordingly, a low GPR56-associated signature is prognostic of a poor outcome in GBM patients even within non-G-CIMP GBMs. Mechanistically, Moreno et al. reveal GPR56 as an inhibitor of the nuclear factor kappa B (NF-κB) signaling pathway, thereby providing the rationale by which this receptor prevents mesenchymal differentiation and radioresistance. A pan-cancer analysis suggests that GPR56 might be an inhibitor of the mesenchymal transition across multiple tumor types beyond GBM [2)].

Unlike in Classical tumors, TP53 is significantly mutated in Proneural tumors (54 percent). Proneural tumors are also characterized by having the most frequent mutations in the IDH1 gene. IDH1, when mutated, codes for a protein that can contribute to abnormal cell growth. Another gene, PDGFRA, was mutated and expressed in abnormally high amounts only in the Proneural tumors and not in any other subgroups. When PDGFRA is altered, too much of its protein can be produced, leading to uncontrolled tumor growth. Unlike the other groups, whose patients were similar in age on average, the Proneural subgroup was significantly younger. They also tended to survive longer. However, patients in the Proneural group who received aggressive treatment did not survive significantly longer than Proneural patients who did not receive aggressive treatment. Clinicians may be able to use this information in the future to avoid unnecessary treatment regimens for patients in the Proneural subgroups.

A retrospective analysis of the AVAglio trial reported 4.3 months incremental survival in the proneural glioblastoma subgroup [3)].

1)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4138801/

2)
Moreno M, Pedrosa L, Paré L, Pineda E, Bejarano L, Martínez J, Balasubramaniyan V, Ezhilarasan R, Kallarackal N, Kim SH, Wang J, Audia A, Conroy S, Marin M, Ribalta T, Pujol T, Herreros A, Tortosa A, Mira H, Alonso MM, Gómez-Manzano C, Graus F, Sulman EP, Piao X, Nakano I, Prat A, Bhat KP, de la Iglesia N. GPR56/ADGRG1 Inhibits Mesenchymal Differentiation and Radioresistance in Glioblastoma. Cell Rep. 2017 Nov 21;21(8):2183-2197. doi: 10.1016/j.celrep.2017.10.083. PubMed PMID: 29166609.

3)
Sandmann T, Bourgon R, Garcia J, Li C, Cloughesy T, Chinot OL, et al. Patients with proneural glioblastoma may derive overall survival benefit from the addition of bevacizumab to first line radiotherapy and temozolomide: Retrospective analysis of the AV Aglio trial. J Clin Oncol. 2015:pii–JCO.2015.61.5005. Epub ahead of print.