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Preview

Proteome-based insights for *IDH*-mutant glioma classification

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In this issue, Bader et al.[1] characterize the proteomes of diffuse glioma brain tumors by liquid chromatography mass spectrometry and classify isocitrate dehydrogenase (IDH)-mutant gliomas into two subtypes, which differ in oncogenic pathways and aerobic/anaerobic energy metabolism.

Diffuse glioma represent a group of aggressive and fatal malignant tumors of the CNS for which current conventional therapies have not significantly improved patient survival. With a median patient survival of 15 months, glioblastoma (GBM) or grade IV glioma either develop *de novo* or derive from a previously diagnosed glioma of lower grade. This distinction in developmental kinetics has suggested the early definition of primary GBM for the former, and secondary GBM for the latter, although both GBM types are undistinguishable from a histopathological point of view.[2]

This visionary distinction has been later supported by the finding of *IDH* mutations as a hallmark for recognizing lower-grade glioma (LGG) and their secondary GBM derivates.[3] Lower-grade glioma originate from either astrocytic lineage, mainly carrying *TP53* mutation associated with *ATRX* mutation, or from oligodendroglial origin, carrying chromosome 1p/19q co-deletion (codel) together with *TERT* promoter mutation, with the former showing earlier median age at diagnosis than the latter (34 versus 44 years).[4–6] The conjunction of genetic features and histopathology had provided the basis for the initial WHO integrative classification of tumors of the CNS in 2016. Of clinical interest, the association of *IDH* mutation with *MGMT* promoter silencing has retrospectively provided a relevance for better benefit of GBM with CpG island methylator phenotype (G-CIMP) to temozolomide therapy.[7]

Regarding primary GBM, initial genetic alterations consist of combined gain of chromosome 7 and loss of chromosome 10, accompanied by *CDKN2A/B* homozygous loss at 9p21 and additional *EGFR* gain at 7p11.[8] Further, compilation of -omics data have provided means to classify those primary GBM into proneural, classical and mesenchymal subgroups.[9] These three -omics profiles being likely to reflect distinct activation modalities of common glioma pathways.

Analyses of CNS tumor methylomes consistently supported the classification of *IDH* mutant glioma into three distinct entities (i.e., lower-grade oligodendroglioma and astrocytoma and secondary GBM) and wild-type primary GBM into three other entities (i.e., proneural, classical, and mesenchymal).[10] This methylomic-based classification has led to a refinement of the WHO integrated classification and is now used as standard of care in daily clinical practice.

However, besides *MGMT* promoter methylation status,[7] no significant advance has been made for the identification of novel predictive biomarkers for glioma therapy. Thus, refined molecular profiling of glioma subsets is strongly needed to provide relevant biomarkers and more accurate diagnostic and ultimately therapeutic tools.

In this issue, Bader et al.[1] describe proteomic and phospho-proteomic analyses of biopsies from 42 representative glioma biopsies with previously established *IDH* and codel statuses.[1] Consistent with their aneuploidies, *IDH* wild-type samples showed increased levels of chromosome 7-encoded proteins and decreased levels of chromosome 10-encoded proteins compared to *IDH* mutant tumors. Surprisingly, molecular relationship revealed that *IDH*-mutants could be divided into two unexpected entities that cluster independently of codel status. This dichotomy was also independent of tumor histopathology and grade; patient age and gender. Indeed, they noticed an entity that showed among others significant accumulation of cancer drivers (CCAR1, SRSF1) with lower abundance of mitochondrial respiratory chain and tricarboxylic acid (TCA) cycle-related proteins (OGDHL) that can presumably cause shorter survival. Although clustering with *IDH*-mutant tumors, this novel entity shared with *IDH* wild types increased levels of oncogenic proteins involved in proliferation (EGFR, AKT2) invasion (CHI3L, S100A10, annexin), angiogenesis (vimentin), inflammatory (STAT1), immunocompetence (MHC I-II), and decreased levels in TCA proteins (HK1).

Applied to glioma biology, genomic, methylomic, and transcriptomic studies have detected chromosomal or local copy numbers variations, promoter methylation, transcription levels and mutations.[6,9,10] Compilation of these data predicted relevant oncogenic activation/inactivation mechanisms and has considerably contributed to WHO CNS tumor classification. By quantitating steady-state protein and phospho-proteins levels, mass spectrometry analysis provides a powerful tool not only to evaluate protein amounts, but also their activation statuses, as a further level of oncogenic regulation. This accurately refines the landscape of oncogenic and metabolic events taking place in glioma development. Thus, besides proposing a novel stratification of *IDH*-mutant gliomas, the differentially expressed proteins and

phospho-proteins unveil a range of single elements from oncogenic pathways such as metabolism, proliferation, invasion, or immunity to be targeted in future therapies.

DECLARATION OF INTERESTS

The author declares no competing interests.

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