EXPERT REVIEWS

Towards developing biomarkers for glioblastoma multiforme: a proteomics view

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Glioblastoma multiforme (GBM) is one of the most aggressive and lethal forms of the primary brain tumors. With predominance of tumor heterogeneity and emergence of new subtypes, new approaches are needed to develop tissue-based markers for tumor typing or circulatory markers to serve as blood-based assays. Multi-omics data integration for GBM tissues would offer new insights on the molecular view of GBM pathogenesis useful to identify biomarker panels. On the other hand, mapping differentially expressed tissue proteins for their secretory potential through bioinformatics analysis or analysis of the tumor cell secretome or tumor exosomes would enhance our understanding of the tumor microenvironment and prospects for targeting circulatory biomarkers. In this review, the authors first present potential biomarker candidates for GBM that have been reported and then focus on plausible pipelines for multi-omic data integration to identify additional, high-confidence molecular panels for clinical applications in GBM.

KEYWORDS: biomarker • cerebrospinal fluid • glioblastoma • mass spectrometry • plasma • proteomics • secretome

Gliomas are the most common brain tumors, originating from the neuroepithelial tissue, of which astrocytomas are the most predominant variety. As per the WHO guidelines, astrocytomas are histologically and clinically classified into four grades (I–IV): grade I (pilocytic astrocytoma) and II (diffuse astrocytoma) are low-grade gliomas that are relatively slow growing, whereas grade III (anaplastic astrocytoma) and glioblastoma multiforme (GBM, grade IV type) are high-grade gliomas, with GBM being the most aggressive tumor characterized by uncontrolled proliferation, diffuse tissue invasion and neurodegeneration [1–4]. Grade II gliomas have a median survival of about 7–8 years, grade III of about 2–3 years, whereas that for GBM is 9–14 months except for rare cases going up to 3 years. GBM accounts for about 50% of all the gliomas diagnosed and primarily occur in adults between the ages of 45 and 70 [5]. They are further grouped into primary GBMs that arise *de novo* without prior history of lower grade disease and secondary GBMs that develop from low-grade gliomas. Primary GBMs comprise more than 90% of the cases, whereas secondary GBMs are less frequent [6]. Despite several overlapping histopathological features, the genetic pathways of the two types of GBMs are quite different and they may have a distinct set of molecular abnormalities [7–9]. Primary GBM predominantly show EGFR amplification/overexpression, *CDKN2A* deletion and *PTEN* mutations and most secondary GBMs are thought to carry *TP53* mutations [10]. Signaling pathways such as receptor tyrosine kinase (RTK) signaling, calcium signaling, mTOR, Notch and Wnt/β-catenin are some of the well-known pathways dysregulated in primary GBM [11,12].

Recent gene expression studies have revealed further heterogeneity among the primary GBM suggesting additional molecular subclasses: neural, proneural, classical and mesenchymal [10,13]. These subtypes were defined on the basis of distinct gene signatures (210 per subtype) and also characterized by different molecular alterations and activated pathways. The classical subtype was found to be characterized by high

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