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Biomarkers of glioblastoma multiforme

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common and lethal primary malignancy of the central nervous system. Modern treatments using surgery and/or chemotherapy and/or radiotherapy are improving survival of patients, but prognosis is still very poor, depending *inter alia* on the patients' individual genomic traits. Most GBMs are primary; however, secondary GBMs have a better prognosis. Aberrant gene expression and copy number alterations make it possible to identify four subtypes: classical, mesenchymal, proneural, and neural. More and more biomarkers continue to be identified in GBM patients. Such biomarkers are related with varying degrees of specificity to one or more of GBM's subtypes and, in many instances, may provide useful information about prognosis. Biomarkers fall into either the imaging or molecular category. Molecular biomarkers are identified by use of such platforms as genomics, proteomics, and metabolomics. In the future, biomarkers, either individually or in some combination, will more reliably identify the pathogenic type of GBM and determine choice of therapy.

1. Introduction

Glioblastoma multiforme (GBM), a World Health Organization (WHO) grade IV glioma, is the most frequent and aggressive malignant primary brain tumor. Patients with GBM have a poor prognosis and the standard first-line of treatment is usually surgery, followed by radiation therapy or combined radiation and chemotherapy. Unfortunately, these treatments are rarely curative and the vast majority of tumors recur locally within the brain. Today, treatment response and tumour recurrence are mainly tracked by MRI and its derivative techniques, including magnetic resonance spectroscopy (MRS). Although these imaging methods are clearly valuable their usefulness is limited. Problems encountered with these monitoring modalities include ambiguous interpretation and forms of pseudoprogression. Unfortunately, reliable early-stage diagnostic biomarkers for GBMs are not yet available.

For reasons such as these, GBM is the prototypical case of a clinical situation in which future therapies will depend on establishing each patient's genotype and proteomic profile of biomarkers, in addition to those provided by neuroimaging. Goals of this kind are being pursued simultaneously with strategies aimed at oncogenic pathways, tumor immunology, angiogenesis, glioma stem cells and epigenomic events [1–3].

It is expected that one or several pathognomonic biomarkers will provide information that will help the clinician make the diagnosis, and allow the neurosurgeon to make the best choice among a wide range of therapeutic options, such as surgery and/or radiotherapy, and/or immunotherapy, or some version of chemotherapy.

In the last few years, increasing numbers of biomarkers have been proposed in the literature. They are listed as imaging or molecular biomarkers, and the latter as genomic/proteomic markers revealed by standard techniques, or those the neurosurgeon can obtain by biopsy.

State-of-the-art biomedical computer technology is essential for revealing causal correlations, particularly in the case of multiple, relatively specific biomarkers.

Because of the increasing importance of biomarkers in the current therapeutic climate, the FDA requires that so-called

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"companion (genomic) tests" that reveal the altered molecules requiring treatment by a drug, always be identified in association with the selected, molecularly appropriate drug.

2. Classification of GBMs

2.1. *Primary and Secondary GBMs*

GBMs can be classified as primary or secondary. Primary GBM occurs *de novo*, whereas secondary GBM develops from an initially low-grade diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III). The majority of GBMs are primary and such patients tend to be older than those with secondary GBM. Secondary GBM is associated with a better prognosis.

Because primary and secondary GBMs evolve from different genetic precursors they show distinctive genetic alterations which make possible reliable molecular differentiation of primary from secondary GBM. In a recent review, Wilson et al. [4] summarize the molecular signatures that can currently distinguish primary from secondary GBMs. As they put it, " … genetic alterations more typical for primary GBM include: a) epidermal growth factor receptor (EGFR) overexpression; b) PTEN mutations; and c) loss of chromosome 10 [5]; whereas, genetic alterations more commonly seen in secondary GBM include: a) isocitrate dehydrogenase-1 (IDH1) mutations; b) TP53 mutations; and c) 19q loss." Among these gene expression patterns the IDH1 mutation has been considered to be the most reliable molecular indicator for differentiating primary from secondary GBM [6].

2.2. *GBM Subtypes*

Based on comprehensive genomic sequence analyses, The Cancer Genome Atlas Research Network (TCGA) cataloged gene mutations and recurrent copy number alterations in relation with GBM. A new classification of GBM tumors into subtypes is founded on distinct biological, imaging and clinical features.

Four subtypes of GBM can be identified. They are based on patterns of aberrant gene expression and copy number alterations. This molecular classification distinguishes the classical, mesenchymal, proneural, and neural subtypes [5,7].

The foregoing classification and subclassification of GBMs currently permit the establishment of a loose correlation between a subtype and certain genetic abnormalities and gene/protein expression changes, followed, in some cases, by the most effective pharmacotherapy. For example, mesenchymal subclass and loss of 17q11.2 will better correlate to tumor necrosis factor (TNF) and treatment with temozolomide and bevacizumab. Evidently, this 'discovery' is of modest importance since these compounds would be recommended in any case; but, the observation is nevertheless encouraging because such therapeutic associations are certainly the most important advantage and the ultimate goal of biomarker research.

Classification is not always easy. As mentioned above, genetic alterations are not common to all areas analyzed, and area-specific and intratumor variations can often be classified into at least two different GBM molecular subgroups. Intratumor heterogeneity of molecular genetic profiles may explain the difficulties encountered in the validation of oncologic biomarkers, and contribute to a biased selection of patients for single target therapies, treatment failure, or drug resistance [8]. The authors summarize the currently available literature on the heterogeneity of GBMs and call attention to the limitation of the routine molecular diagnostics and personalized therapy.

2.3. *Molecular GBM Biomarkers*

(i) Loss of 1p, 19q and 10q heterozygosity: 10q loss can be found alone or together, with loss of heterozygosity on chromosomes 1p and 19q. It was shown that 10q loss of heterozygosity predicted a survival disadvantage in patients with oligodendroglioma or with grade II or III GBM [9,2].

(ii) IDH1 or IDH2 mutations: The detection of mutations in the metabolic enzyme isocitrate dehydrogenase isoforms, IDH1 or IDH2, in the vast majority of WHO-classification grade II or III gliomas, and in the secondary glioblastomas that develop from these precursors, provides a biological basis for a clinical categorization. IDH1 mutations are an early event in tumorigenesis. They offer useful clues for diagnosis of a specific subgroup of glioblastomas. They are the best available genetic hallmark of secondary GBMs, which usually have a more favorable prognosis [10,11]. 2-Hydroxyglutarate (2HG) production can also be used as a marker of IDH1 and IDH2 mutations. If 2HG levels are high in the serum, urine, or cerebrospinal fluid of patients with IDH-mutated cancers, measurement of this metabolite could be used, either instead of, or as an adjunct to, histopathological analysis—a more invasive diagnostic procedure [11].

(iii) Patients with GBM show increased expression of epidermal growth factor, latrophilin, and '7- transmembrane domain-containing' protein 1 on chromosome 1 (ELTD1), which is associated with increased angiogenesis, a higher tumor grade, a worse prognosis, and shorter survival [12].

(iv) In patients with GBM, after a standard treatment (surgery, radiotherapy, chemotherapy), increased serum YKL-40 expression, if it correlates with RMI data, provides additional and earlier information and serves as a further aid in establishing the prognosis [13].

(v) The H3F3A gene encodes histone H3.3 and it occurs in high-grade thalamic gliomas that arise at midline locations, including the pons, thalamus, and spine. In particular, this mutation is found mainly in tumors in children and adolescents, and also in young adults [14].

(vi) Phosphate and tensin homolog deleted on chromosome ten (PTEN) acts as a tumor suppressor gene through the action of its phosphatase protein product. Cytogenetic and loss of heterozygosity studies have suggested the presence of at least one tumor suppressor gene on chromosome 10 involved in the formation of high grade gliomas. The PTEN gene, also termed