

Studies on genetic and epigenetic mechanisms of carcinogenesis have led to the discovery of crucial genetic events for many of particular malignancies. This was followed by invention of new therapeutic approaches based on molecular mechanisms underlying cancer development and progression that bears the name of personalised medicine. In the case of gliomas, ascertainment of genetic/epigenetic markers was the basis for re-classification of tumours that until now depended on histopathological analysis. This article reviews recent advances in personalised medicine and the new World Health Organisation classification of gliomas.

**Key words:** gliomas, epigenetic mechanisms of carcinogenesis, personalized medicine.

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# Personalized medicine in oncology. New perspectives in management of gliomas

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Personalized cancer medicine is based on molecular profiling of cancer cells. Defining genetic alterations, aside from establishing a precise molecular diagnosis of the tumour and predicting the course of the disease, allows granting an individual patient tailored therapy in accordance to genomic as well as epigenomic characteristics of the tumour [1]. A better understanding of molecular mechanisms underlying cancer development and progression has enabled the development of new therapeutic schemes aimed precisely at particular protein products of pivotal genes [2]. Nowadays, these therapeutic procedures are becoming standard management for an increasing number of cancers [1]. Alterations such as *ERBB2* (*HER2*) amplification in breast cancer, *EGFR* mutations in non-small cell lung carcinoma, *KRAS* and *BRAF* mutations in colorectal cancer or *BCR-Abl* fusion in chronic myelogenous leukemia are routinely examined. Targeted cancer therapies, which emerged from the results of these studies permitted an increase of treatment effectiveness in oncological patients [2, 3].

Immense progress in our understanding of cancer genetics was made possible through development of molecular techniques. Availability of large scale molecular approaches like next generation sequencing (NGS) and array techniques for chromosomal instability, gene expression or methylation pattern allowed to identify vast numbers of different genetic alterations in each malignancy. These analyses allowed in turn establishing key genetic features to employ as biomarkers for optimization of cancer patients treatment [4].

The significance of personalized medicine is well illustrated by an innovative approach to classification of gliomas published in 2016 by World Health Organization (WHO) [5]. Previous classification of gliomas (WHO, 2007) was based on histologic criteria such as microscopic analyses of hematoxylin and eosin stained cancer specimens, immunohistochemical evaluation of expression of selected proteins and ultrastructural cell differences [6]. These classical approaches proved in discordance with the molecular mechanisms of tumour development and progression and thus did not open the possibility of targeted clinical management of cancer patients [5, 6].

Current revolutionary diagnostics of brain tumours employs both histologic and molecular testing. Clinical utility as prognostic or predictive markers has been proven for mutations in genes such as: *IDH1/IDH2* (isocitrate dehydrogenase 1 or 2 genes), *ATRX* (alpha-thalassemia/mental retardation syndrome X-linked), *TERT* (telomerase reverse transcriptase) promoter mutations as well as *TP53* mutations and 1p/19q co-deletion. Moreover, methylation of the promoter of *MGMT* (O6-methylguanine-DNA methyltransferase) was found to be an interesting predicting marker of response to alkylating agents which are routinely used as chemotherapy of gliomas as well as a marker of potential response to radiotherapy [5].

Our current knowledge of genetic markers of gliomas results from long-term studies that showed alterations crucial for development and progres-

sion of gliomas' including wide spectrum of genetic changes such as chromosomal aberrations, gene mutations and epigenetic silencing. DNA copy number variations (CNVs) occurring during cell division that result in genomic deletions/duplications belong to the most important mechanisms of tumour suppressors loss-of-function and proto-oncogenes gain-of-function [2]. Array Comparative Genomic Hybridization (aCGH) studies uncovered that the most frequent CNVs in gliomas are 1p, 9p, 10, 10p, 10q, 13q, 19q, 22q deletions and 7q gains. These studies allowed also to establish a characteristic profile of chromosomal aberrations in gliomas and thus enabled identifying a progression pattern from low to high grade gliomas [2].

*IDH1* and *IDH2* gene mutations are widely reported in gliomas. *IDH1* plays a role in citric acid pathway while *IDH2* variants are reported to influence angiogenesis, apoptosis and glucose metabolism [2]. Mutations in codon 132 and 172 in *IDH1* and *IDH2*, respectively, occur in about 70% of diffuse astrocytic and oligodendroglial gliomas as well as in secondary glioblastomas [4]. *IDH* mutations are associated with initiation of carcinogenesis in grade II diffuse astrocytomas and grade III anaplastic astrocytomas which are now classified as either: i) *IDH*-mutant, ii) *IDH*-wildtype and iii) not otherwise specified (NOS).

*TP53* and *ATRX* gene mutations are a driving force in diffuse and anaplastic astrocytomas while 1p/19q co-deletion [resulting from an unbalanced translocation t(1;19)(q10;p10)] and *TERT* promoter mutation in oligodendrogliomas [4, 5]. These two different molecular pathways comprise a criterion for distinguishing between astrocytic versus oligodendroglial tumours.

In contrary to diffuse and anaplastic astrocytomas as well as secondary glioblastomas, *IDH*-wildtype status is characteristic for 90% of primary glioblastomas (the most frequent central nervous system tumours) [5]. Thus, mutations in *IDH* gene family in glioblastomas are currently accepted as an important diagnostic, predictive and prognostic biomarker.

Furthermore, in *IDH*-wildtype glioblastomas genetic alterations such as copy number gains of chromosome 7, monosomy of chromosome 10, mutations in *PTEN*, homozygous deletion of *CDKN2A/p14<sup>ARF</sup>*, *CDKN2B* and *TERT* promoter mutations are frequently observed. Moreover, mutations in *TERT* promoter have been shown to correlate with patients' survival expectations depending on other genetic alterations such as *IDH* mutation status, 1p/19q co-deletion and *EGFR* amplification [2].

Methylation status of *MGMT* was found to be a promising predictive marker for high grade gliomas. *MGMT* plays an important role in DNA base excision repair [7]. Thus, *MGMT* promoter hypermethylation (leading to gene expression downregulation) results in ineffective reparation of DNA alkyl-adducts and in turn, correlates with an enhanced response to both, chemotherapy employing alkylating agents and to radiotherapy [7].

However, as coexistence of *MGMT* promoter hypermethylation along with 1p/19q co-deletion and *IDH1* mutations is frequent in secondary gliomas, it remains unclear which of those genetic events has a more causative role [2].

Recently, several other genetic alterations have been found in gliomas and seems to be a potential new predictive and prognostic biomarkers. Mutations in *BRAF*, H3-K27M and *EGFRvIII* and fusion of *FGFR-TACC* will enable to develop better therapeutic strategies [4].

Recent WHO 2016 classification of gliomas has opened up new possibilities in personalized therapy and allows a better understanding of pathogenesis and mechanisms of drug resistance.

Lately, a high potential of a possibility of non-invasive glioma diagnosis before tailored therapy has been also attributed to liquid biopsy.

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