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Role of Host Genetic Factors in Patients with Astrocytomas

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Abstract

Brain tumor is abnormal growth of cells in or around the brain. Prevalence of brain tumor that metastasizes is one-fourth of all type of cancer. In cancer patients, chances of generation of metastatic brain tumors is 10-15 per one lac. The occurrence of malignant gliomas is around 5 to 10% in the same population. In malignant glioma, the different pathway is involved in development and progression. It carries a bleak prognosis and often recurs even after standard treatment modalities. Wnt signaling pathway, growth factors, MMPs/TIMPs and drug metabolizing enzyme genes have been reported to show a role in the initiation, progression, and metabolism of drugs in patients with brain tumor. Hence, the aim of this review is to briefly discuss the impact of genetic and epigenetic variations within Wnt signaling pathway, matrix metalloproteinases (MMPs), growth factors, cytokines and drug metabolizing enzyme genes in patients with brain cancer. Description of certain inherited and acquired genetic variations in the genes involved in the initiation, progression, and metabolism of drugs within a given individual will be important to improve the choice of medication in astrocytoma patients. These studies can be useful to design the future prognostics, diagnostics for global health and rational therapeutics on the critical path to personalized medicine. Till now, the variations in genes associated with initiation, progression of tumor in response to drugs in patients with brain cancer has not been described well. Hence, further research is required to study genetic variations of these genes in patients with brain cancer and its correlation with the pathologic grade, proliferation, invasion and prognostic significance.

Keywords: Genetic predisposition; Wnt signaling gene; MMP; Cytokines; Growth factor; Drug metabolizing enzyme gene; Polymorphism; Epigenetics

Introduction

The abnormal growth of cells in and around the brain are of two types, primary and secondary (metastatic). Prevalence of metastatic brain tumor is one-fourth of all cancers. In adult cancer patients, 10-15% occur as primary tumor and they can convert into metastatic brain tumor at any point with the prevalence of 10-15%. Gliomas mostly primary tumors [1] can convert to malignant gliomas with the prevalence of 5 to 10 per 1,00,000 cancer patients [2]. Brain cancer patients have been diagnosed with astrocytomas, oligodendrogliomas, ependymomas and mixed oligoastrocytomas. In all brain cancers, Glioblastoma multiform (GBM) with the prevalence of 2% of malignant tumors is the main reason of mortality and morbidity in patients of brain cancer. Epidemiological studies suggested that inherited polymorphisms in genes related to carcinogen metabolism, oxidative metabolism and DNA repair is an independent risk factor. Genetic studies showed that most human gliomas appear to have a set of pathways that are disrupted (pRb, p53, PTEN) and a set that is abnormally active (telomerase, EGFR, Akt). However, the molecular mechanisms of development and progression of gliomas needs to be studied. As reported in literature, Wnt signaling pathway has a role in cancer development, cell proliferation, and invasion. Emerging evidence suggests that persistent activation of β-catenin has a significant role in variety of human cancers including glioma. Deregulation of Wnt signaling pathway is associated with brain tumors, including gliomas. Apart from the Wnt signaling pathway, growth factors, cytokines including MMPs plays role in cellular proliferation, angiogenesis, invasion, and metastasis of glioma. Each individual has unique genetic makeup. Variations in Wnt signaling pathway, growth factors, cytokines and MMPs/TIMPs genes in patients of brain cancer explain a patient's risk which can be used in identifying novel drug target for brain cancer therapy. In recent therapies temozolomide act as a genotoxic drug in combination with signaling and pharmacological inhibitors are available. No therapy is successful for the treatment of glioma patients [3]. So far, the gene encoding for genetic and epigenetic variation associated with initiation, progression of tumor in response to drugs has not been described well. Hence the aim of this review is to discuss in brief impacts of Wnt signaling pathway, cytokines including MMPs and drug metabolizing enzyme genes in pateints with brain cancer.

Methodology

Literature was accessed and reviewed with the keywords like brain cancer, glioma, astrocytoma, development and progression of glioma, polymorphism of MMPs, Wnt signaling pathway, cytokine, and drug metabolizing enzyme gene in respect to patients of brain cancer using pub med and Google search.

Polymorphism

In the study of polymorphism, gene selection basis should be 1) from any pathways which are considered to be involved in the progression of brain cancer 2) with evidence of polymorphism in high frequency so that its impact on any disease or brain cancer on population can be used for the treatment of brain cancer 3) polymorphism of gene alter some of the biological function.

The matrix metalloproteinases (MMPs) are endopeptidase, an enzyme that degrades extracellular matrix composed of macromolecules. MMPs enzyme is responsible for invasiveness of tumor cell and colonization of secondary sites which are controlled mainly by pro-enzyme activation, at gene transcription level and by tissue inhibitors (TIMPs). Multiple MMPs can be expressed by tumor and/or host stromal cells. Increased levels of MMPs are frequently detected in brain and neck cancer tissues and are often associated with poor prognosis [4,5]. Potential role in proliferative signaling by regulation of autocrine growth factor release [6,7].

Stojic et al. [8] reported that MMP1, MMP11 and MMP19 gene has the main role in the occurrence and development of astrocytic tumors and can be a promising site for treatment as well. MMP-2 promoter region (C/T-1306) SNP has less promoter activity. MMP2, astrocyte factors, and ERK1/2 signaling pathway are involved in brain metastases [9]. Rome et al. [8] described that MMP-7 mRNA expression was highly variable within glioma patients and polymorphism in MMP-2 (-1306C/T) gene was not involved in the development of GBM [10]. The main pathway which is involved in the generation of all type of cancers, is the Wnt/beta-catenin/Tcf signaling pathway which is less involved in glioma malignancy [11]. Differentiation of dopaminergic neurons and hippocampal neurogenesis has been promoted by astrocytes and are good ligand of Wnt [12]. In adults, the Wnt/β-catenin pathway gene is widely expressed and regulate the brain development by neurogenesis, cellular proliferation, and axis polarization [13]. In the astrocytic tumor, the main activated pathway is the Wnt/beta-catenin/Tcf signaling pathway [14]. In bipolar patients, GSK3B CC and CT genotype are well treated with lithium prophylaxis than TT genotype and neuroprotection in CNS is mainly by the Wnt/β-catenin pathway [15]. Some studies reported the glioblastoma progression is regulated by deregulation of Wnt/β-catenin/Tcf signaling pathway and malignant tumors are inhibited by Nonsteroidal anti-inflammatory drugs (NSAIDs) [16]. Heterozygosity in the AXIN2 (chromosome 17q23-q24) gene is associated with the breast cancer patients, neuroblastoma, and other tumors. The mutation in this gene activates the Wnt signaling pathway in medulloblastomas [17,18]. Other study performed by Warrier et al. [19] reported that FRP4 could prove a good target for effective therapy of brain tumors. Wnt signaling pathway may help provide new biological insights, can be helpful in identifying common drug targets. GSK-3 β is approved a good therapeutic target for cancer treatment [20-21] and p53-dependent activation of Bax is regulated by modulation of GSK-3β, results in loss of mitochondrial membrane potential and release cytochrome C and caspase-9 processing [20]. GSK-3β exerts a pro-apoptotic role and has been found to play a critical activator role of cell death in numerous models of neuronal apoptosis and GSK-3β inhibition enhance cell survival [22-23]. Various studies suggested that the Wnt/β-catenin pathway has a role in the development of different tumors but has less involved in glioma occurrence and development [24]. A recent study described the role of epidermal growth factor receptor in glioma occurrence and development which could be a good target for therapeutic purposes.

Cytokines are glycoproteins which modulate the cell activities by binding to specific receptor ligand and results in signal transduction and activation of secondary pathways. After gene activation, it speeds up the mitotic division, growth, differentiation and migration. Tumour cytokine is rich in inflammatory cytokine and growth factor but do not have specific and sustained immune response. Tumor cytokine and growth factor speed up the tumor growth and suppression than an effective host antitumor response. Hadjigeorgiou et al. [25] reported the presence of IL-1RN allele 2 is associated with brain hemorrhage. A IL-1β -511 gene in the promoter region when shows functional biallelic polymorphism then it isassociated with susceptibility to the severity of various central nervous system (CNS) disorders [26-28]. In another study, TNF-a gene is considered to be a cause for generation of neurological diseases [29-31] in brain tissue produced by astrocytes. In in-vitro studies, TNF-αhas been involved in demyelination of nerve fibers [32] and showing cytotoxic effects on myelin-producing oligodendrocytes [33-34]. Schmidt formed different clones of canine glioma cells which secretes different amounts of PDGF and TGF-β correlated with in-vitro cloning efficiency and in-vivo tumorigenicity [34].

Epigenetics

Unlike the genome, an organism's epigenome can be modified by the environmental factor, including drug therapy. Much of inter-individual variation in pharmacokinetics related gene has been attributed to the difference in expression of genes. Many, but not all, of these differences in expression are explained by genetic polymorphism. Other factors like gene cis- and trans-acting transcriptional components, alternative splicing, expression of regulatory RNAs, epigenetics DNA methylation and histone modifications, gene expression affects phenotype variation [35]. The difference in the DNA methylation status of genes and allele-specific single nucleotide polymorphisms (SNPs) affect the expression of associated genes and can result in an inter-individual difference in progression and drug response [36]. Phenotypic variability is nothing but an expression differences of two alleles between two individuals. It can predict the development, progression and drug responses in patients with brain cancer.

Haplotype, genetic variants are used to predict genotype-phenotype correlation. Transcription is affected by DNA sequence variations and heritable changes in gene expression affect the progression of disease, toxicity and drug response. Many genes encoding drug metabolism enzymes (DMEs) [37], drug transporters [37], drug targets and nuclear transcription factors [38] could be under epigenetic control. With epigenetic control, gene expression could be altered to affect drug efficacy and drug toxicity [39-42].

Molecular signatures will prove useful target due to genotype and phenotype link for "target organ toxicity patterns" and can act as a biomarker of differential susceptibility and exposure at early stage.

Toxicogenomics is a new tool for genomics and proteomics study to understand drug toxicity. The drug induces morphological changes at protein as well as gene level [43]. Metabolic profiles of toxicologic exposures have yielded many potential markers of early effects. Findings of toxicogenomics study of drug metabolizing enzyme genes may be helpful in "personalized" to tailor drug treatments based on patients' toxicity profiles.

The toxicogenomics is useful to study toxicology predication difference from in-vitro models to in vivo and other assay methods using fluorophores and DNA microarrays etc.

Pharmacogenetics

Currently, ongoing pharmacogenomic studies have found evidence of drug response variation due to inter-individual genetic variation [44]. The genotyping technology provides the accessible data which

could be further used to study gene-drug interaction [45]. Hence there is an urgent need to establish the predictive pharmacogenetic testing and genotyping to study the drug response differences with a goal to better personalize drug therapy [45].

Indian population represents global diversity shaped by multiple waves of migration and local admixture events. Evidence suggests that the genetically distinct Ancestral North Indians and Ancestral South Indians admixed, leaving traces of their ancestry in virtually all of the country's current population. Even though, populations across the country appear to have become more and more differentiated from one another with the establishment of India's caste system and the subsequent onset of endogamy, a decline in inter-mixing that has contributed to some of the features found in Indian populations today which includepopulation-specific differences in susceptibility to some diseases. Inter-individual response to drugs in disease patients greatly varies because the genetic background of the population is different. The drugs used in the treatment of diseased individuals have clinical implications resulting in genetic polymorphisms of pharmacokinetics related genes. The response and efficacy of the drugs are depending on the metabolism of drugs. Some patients respond well while certain patients develop adverse effects such as liver, kidney, CNS, gastrointestinal, cardiac toxicity etc. However, there is no approach to predict the drug response in diseased individuals. The clinical assessment for efficacy and toxicity of the drug in diseased individuals are difficult but are the first indication of treatment failure resultantingin patient's demises. As of now, there is no available biomarker to monitor the response of drug and its outcome to brain cancer patients. Hence, further studies are required to describe the genetic and epigenetic variations of drug metabolizing enzymes gene in patients with brain cancer on chemotherapy. These studies can be helpful to identify the predictor or biomarker to drug response and its outcome.

Discussion

Significance

Development of genetic tests has been proven to be useful for optimizing drug efficacy with reduced toxicity in patients with brain cancer. With genotyping data, it's easy to identify the patient's which are at high risk of progression of brain tumor with longer induction period. Genotyping of drug metabolizing enzyme and related genes might predict and guide the therapeutics in patients with brain cancer.

Future Challenges

CNS malignancies are oligodendrogliomas, astrocytomas and meningiomas. Astrocytomas could be the type of (grade I) pilocytic, (grade II) diffuse, (grade III) anaplastic, and (GBM, grade IV) glioblastoma multiforme. GBM patient after diagnosis survives approximately 12 months. GBM patients after aggressive surgical therapy followed by radiotherapy and with all chemotherapeutic agents are not effectively treated. Presently in development of any new therapy which is multipronged need an in-depth understanding of the principle of malignant cell survival and growth. The major challenge in GBM treatment is the blood-brain barrier which affects drug delivery and narrow window of surgical option. Radiation therapy is curative therapy however there is a need of designing better chemotherapeutic agents targeting glioma appropriately [46].

Further studies are required to explore the genetic and epigenetic variation associated with development, progression and drug response in patients with brain tumor. Wnt signaling pathway, growth factor, cytokine, MMPs/TIMPS and drug metabolizing enzyme genes may provide insights to customize disease-prevention strategies in patients with brain cancer.

Summary

Such kind of studies can be helpful in finding the drug target, predictor, and biomarker for drug response to brain cancer patients.

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