PharmGKB Summary: Pharmacogene Information for *MGMT*

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The *MGMT* (O^6-methylguanine DNA methyltransferase) gene is located on chromosome 10q26 and encodes a DNA-repair protein O^6-alkylguanine DNA methyltransferase. The protein repairs the mutagenic DNA lesion O^6-methylguanine to guanine by removing alkyl groups from DNA alkylation sites. This, in turn, prevents mismatches and errors during DNA replication and transcription leading to mutagenesis. MGMT is one of the few known proteins in the DNA Direct Reversal Repair pathway in mammals [1]. The restoration of the DNA consumes the MGMT protein, which the cell must replenish. Loss of the MGMT gene, or silencing of the gene through DNA methylation in the promoter region, may increase the carcinogenic risk after exposure to alkylating agents. Similarly, high levels of MGMT activity in cancer cells create a resistant phenotype by blunting the therapeutic effect of alkylating agents and may be an important determinant of treatment failure [2]. Genetic variants in MGMT as well as DNA methylation in the MGMT have shown to influence patient risk in several cancers. This review will focus on the pharmacogenomics of MGMT, as well as its importance as a clinical biomarker to predict patient survival and determine therapy in cancer patients.

Pharmacological agents that interact with MGMT

Alkylating agents are often used to treat several cancer types, as they destroy the DNA in tumor cells through alkylation by introducing cross-links, hence preventing further division and lead to cell death. However, the role of MGMT is to remove such alkyl groups from alkylated DNA strands and lead to DNA repair. Overexpression of MGMT has shown to increase the resistance to nitrosoureas (e.g. streptozotocin) and temozolomide in melanoma cells, with a 3-fold increase in their IC_{50} values [3]. On the other hand, MGMT also increases the sensitivity of mitomycin C by 10 folds in melanoma cells, the mechanism for which is unknown. It has been shown that phenytoin treatment may increase the methylation capacity in the brains of animals [4]. It has been hypothesized that phenytoin may methylate the CpG islands in the promoter region in MGMT and may increase the efficacy of temozolomide through synergy [5]. On the other hand, MGMT has shown not to affect the sensitivity of busulfan [PA165374494, 4] that is used to treat leukemia, as it may be inducing lesions in the N^7 region instead of the O^6 region of guanine.

MGMT Pharmacogenomics

Lung Cancer

Lung cancer is the second leading cause of death in the USA, with tobacco smoking being a major causative factor. Single nucleotide polymorphisms (SNPs) in protein-coding regions of the DNA repair genes can plausibly affect DNA repair capacity, and hence affect the level of genetic damage resulting from exposure to carcinogens in tobacco smoke. *Hill et al.* evaluated the genotype-phenotype relationship between two SNPs, L84F and I143V, in the MGMT gene, and

the increased sensitivity to genetic damage induced by the alkylating tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [6]. Nitrosamines induce the formation of O^6-alkylguanine adducts, that are mainly repaired by the protein MGMT. Chromosome aberration (CA) frequencies were measured in the lymphocytes from 114 volunteers exposed to NNK. A significant increase in NNK-induced CA frequency was observed in cells with the L84F polymorphism, and I143V polymorphism, compared to cells homozygous for wild alleles (*p*-value < 0.02). Significant positive interactions between these SNPs and smoking, gender and age were also observed (*p*-value < 0.03). Individuals who inherited two SNPs had significantly higher levels of NNK-induced CA compared to individuals with none or with only one SNP (*p*-value < 0.002). Hence, L84F and I143V SNPs may alter the function characteristics of the MGMT protein, resulting in suboptimal repair of genetic damage induced by NNK [6].

Breast Cancer

Breast cancer affects 1 in 8 women during their lives. As MGMT is involved in the DNA direct reversal repair pathway, variations may also affect breast cancer treatment. To test this hypothesis, *Shen et al*. genotyped three variants in the protein-coding regions of the MGMT gene - L84F, I143V and K178R over a cohort of 1067 cases and 1110 controls [7]. While individually, there were no main effects between any variant genotype, haplotype or diplotype and breast cancer risk, associations in concordance with other factors were observed. Heavy smoking significantly increased breast cancer risk for women with the codon 84 variant T-allele (odds ratio, OR = 3.0). An inverse association between fruits and vegetables consumption and breast cancer risk was observed among women with the wild-type genotype for codon 84 (OR = 0.8), or with at least one variant allele for codon 143 (OR = 0.6). Hence, polymorphisms in MGMT may modulate the associations observed between consumption, smoking and breast cancer risk.

Glioblastoma Multiforme

Glioblastoma Multiforme (GBM), a malignant brain tumor, is among the most lethal of all cancers [8]. Temozolomide is currently being used to treat patients diagnosed with GBM. However, MGMT expression may severely impact the sensitivity of temozolomide, and hence affect overall patient survival. The promoter region of the MGMT gene may be methylated, hence silencing the MGMT gene [9]. For testing of the MGMT promoter methylation status in the clinical setting, DNA-based methods such as methylation-specific polymerase chain reaction (MS-PCR) or pyrosequencing are preferred. *Butowski, et al*. tested the MGMT promoter methylation status in 66 patients treated with temozolomide. They found that unmethylated MGMT was associated with increased hazard for early death (Hazard ratio, HR = 5.19) and early risk to progression (HR = 3.07) [10]. *Brown et al*. conducted a GWAS study to find that one SNP in the MGMT gene, Rs531572, was highly significantly associated with both IC_{50} values ($\log_{10}$ *p*-value < -6.4) and *MGMT* transcript levels ($\log_{10}$ *p*-value < -25) with the A allele associated with that higher IC_{50} values and greater *MGMT* transcript levels [11].

Conclusion

An extensive review of research articles needs to be further carried out to further understand and delineate the pharmacogenomics of the MGMT gene and its promoter region. As it seems to be

statistically associated with three of the most devastating cancer types, understanding the pharmacogenomics may aid towards development of better prognostic and therapeutic methods.

References:

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