GENETICS

Polymorphism in the Tumor Necrosis Factor Alpha Promoter Region and Its Influence on Colorectal Cancer Predisposition Risk in Malaysian Population

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ABSTRACT

Objective: **A case control study was designed to investigate the TNF-α -308 G>A polymorphism allele frequencies and to determine the influence of the polymorphic genotype on sporadic CRC susceptibility risk in Malaysian population.**

Materials and Methods: **Peripheral blood samples of 164 normal controls and 161 clinically and histopathologically confirmed CRC patients were genotyped for TNF-α -308 G>A polymorphism employing allele specific PCR. The relative associations of various genotypes with CRC susceptibility risk was determined by calculating Odds Ratios. Corresponding chi-square tests on the CRC patients and controls were carried out and 95% confidence interval (95% CI) were determined using Fisher exacts tests.**

Results: **On comparing the frequencies of genotypes of patients and controls, the homozygous variant AA was significantly higher in CRC patients (p = 0.030) compared to controls. On investigating the association of the polymorphic genotypes with CRC susceptibility risk, the homozygous variant TNF-α -308 AA showed significantly increased risk with OR 2.5842.**

Conclusion: **Our results suggest that, polymorphic genotype of inflammation response gene TNF-α is significantly associated with CRC susceptibility risk and could be considered as a high risk variant for CRC predisposition.**

KEY WORDS

colorectal cancer, inflammation response gene, TNF- α , plymorphism

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in developed countries and getting more and more attention in developing countries for its morbidity and mortality. Even though the definite mechanism of development is still unknown, both environmental factors and genetic susceptibility are believed to contribute to the onset of CRC. Excluding inherited types of CRC, the susceptibility of a certain individual to development of sporadic CRC remains largely undetermined. A recent leading theory is that the oxidative stress that accompanies chronic inflammation contributes to neoplastic transformation[1,2] Epidemiological observations, animal and clinical studies have established an association between continuous inflammatory condition and CRC[1,3,4] Patients with inflammatory bowel disease (IBD), including Crohn's disease (CD) and Ulcerative colitis (UC), are at increased risk of developing colorectal cancer[5]. The associations between inflammatory response genes and IBD make them attractive candidate susceptibility genes for colorectal cancer since approximately 1:6 individuals with IBD will develop malignancy[6]. Despite these evidences strongly implicating chronic inflammation as a culprit in colorectal carcinogenesis, surprisingly little research has directly addressed the genetic predisposing factors which mediate inflammatory response and favors CRC development.

Genetic polymorphisms have emerged in recent years as important determinants of disease susceptibility and severity. Polymorphic variants of several genes are thought to play a key role in determining how individuals respond at the cellular level to various environment conditions including inflammation. If inflammation constitutes one of the molecular networks underlying susceptibility to CRC, genes which mediate inflammatory response might be a group of candidate

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