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Review

Nucleotide excision repair related gene polymorphisms and genetic susceptibility, chemotherapeutic sensitivity and prognosis of gastric cancer

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ABSTRACT

Human genomic DNA is in a dynamic balance of damage and repair. Cells employ multiple and specific repair pathways, such as nucleotide excision repair (NER), as unrepaired DNA damage has deleterious consequences and could give rise to carcinogenesis. Gene polymorphisms play a crucial role in predicting the risk and prognosis of cancer. Polymorphisms of NER-related genes could alter the ability of NER to effectively monitor and repair DNA damage, and thus may be associated with genetic susceptibility, chemotherapeutic sensitivity and prognosis of cancer. In recent years, increasing studies have focused on the association between polymorphisms of NER genes and gastric cancer, the world's fourth most common cancer and the second most common cause for cancer-related death. Here we reviewed the recent studies on the associations between polymorphisms of NER genes and gastric cancer from perspectives of genetic susceptibility, chemotherapeutic sensitivity and prognosis.

Contents

Abbreviations: NER, nucleotide excision repair; GC, gastric cancer; BER, base excision repair; MMR, mismatch repair; DSBR, double-strand break repair; GGNER, global genome nucleotide excision repair; TCNER, transcription-coupled nucleotide excision repair; GCA, gastric cardiac adenocarcinoma; UV, ultraviolet; RFS, relapse free survival; OS, overall survival; UTR, untranslated regions; PFS, progression free survival; ROS, reactive oxygen species; EBV, Epstein-Barr virus.

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1. Introduction

Gastric cancer (GC) is the world's fourth most common cancer and the second most common cause of cancer-related death [1]. As a complex disease, GC is influenced by genetic predispositions, living habits and environmental factors [2]. Studies have suggested that different individuals bear different GC risk even under similar environmental conditions [3]. Chemotherapy and adjuvant chemotherapy are critical to improve the prognosis of GC, but individuals exhibit different chemotherapeutic responses and clinical outcomes [4]. One of the most important reasons for these variations among individuals may be the involvement of key gene polymorphisms in the initiation, progression and treatment of GC. Identifying GC susceptibility related gene polymorphisms is critical for the identification of individuals with high GC risk. Furthermore, finding gene polymorphisms related to chemotherapeutic sensitivity and prognosis of GC could largely benefit the development of an individualized GC chemotherapeutic regimen and the control of GC metastasis and recurrence, thereby increasing GC chemotherapeutic efficiency and improving prognosis.

DNA repair systems play a pivotal role in maintaining the stability and integrity of the genome [5]. These systems include nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR) and double-strand break repair (DSBR) [6]. NER is a critical and versatile system that monitors and repairs a variety of DNA damage, including UV-induced cyclobutane pyrimidine dimers, bulky adducts and DNA crosslinks [7]. NER is composed of global genome nucleotide excision repair (GGNER) and transcription-coupled nucleotide excision repair (TCNER). TCNER specifically repairs the transcribed strand of the gene possessing transcriptional activity and ensures the transcribed strand of the active gene to be repaired preferentially than the other sites of the genome [8]. GGNER manages DNA damage of other regions, including noncoding regions, silenced genes and the non-transcribed strand of actively transcribed genes [9]. The NER steps include damage recognition, damage demarcation and unwinding, damage incision and new strand ligation. Each step requires corresponding functional proteins, and more than 30 factors are involved in this complex and precise process, including XPA, XPB, XPC, XPD, XPE, XPF, XPG, CSA, CSB, RPA and ERCC1 [10].

Defective NER in humans was originally related to rare autosomal-recessive inherited diseases, such as xeroderma pigmentosum (XP) and Cockayne syndrome (CS) [10]. XP is characterized by defective DNA repair and a markedly increased risk of skin cancer that is associated with exposure to a particular environmental carcinogen, ultraviolet radiation [11]. CS patients also experience increased sun sensitivity, like XP patients. In contrast to XP patients, however, CS patients do not exhibit an increased skin cancer risk [12]. The most common feature in XP and CS is genetic defects specifically mutation of NER enzymes, leading to a reduction in or abolishment of NER [13]. In recent years, emerging evidence has indicated that defective NER is also related to multiple aspects of cancer.

Cellular DNA is constantly under damage from endogenous and exogenous stimuli, leading to a dynamic cellular balance between damage and repair. Unrepaired DNA damage would have deleterious effects to normal functions of cells and could contribute to the initiation of cancer [14]. Defects in NER would increase the instability of genome, and unrepaired DNA damage may thereby enhance genetic susceptibility to GC and give rise to gastric carcinogenesis [15]. Any changes in NER function would also influence the repair of DNA damage caused by chemotherapeutic drugs. Platinum-based chemotherapeutic drugs, for example, induce apoptosis of cancer cells by forming DNA adducts [16] that are recognized and repaired by NER. Therefore, disruption of the NER system would alter the chemotherapeutic sensitivity and prognosis of cancer patients, including those with GC. Polymorphisms of NER genes could further alter NER by influencing the expression and function of key proteins in NER. Thus, NER gene polymorphisms might be associated with genetic susceptibility, chemotherapeutic sensitivity and prognosis of GC.

In recent years, increasing studies have focused on the association of NER gene polymorphisms with the occurrence, development and treatment of GC. Here we review recent studies concerning NER gene polymorphisms and GC from the perspectives of genetic susceptibility, chemotherapeutic sensitivity and prognosis.

2. NER-related gene polymorphisms and genetic susceptibility of GC

2.1. DNA damage recognition-related NER polymorphisms

The recognition of DNA damage is indispensible for the initiation of NER. The NER system recognizes DNA damage by sensing the DNA distortion rather than via specific enzymes, as is the case for BER [17]. In mammals, the distortion-recognizing factor is a heterotrimeric complex composed of XPC, RAD23 and centrin-2 [18]. RAD23 and centrin-2 stabilize this complex and ensure NER capacity [19,20]. UV-induced DNA damage is recognized by the heterodimeric complex UV-DDB consisting of DDB1 and DDB2 [21]. In TCNER, RNA polymerase II blocked at the site of DNA damage triggers other factors to assemble together with CSB (ERCC6) and CSA (ERCC8) [22,23]. CSB is a DNA-dependent ATPase [24] and CSA is part of a ubiquitin ligase complex [25]. Until now, only the associations of *XPA* and *XPC* with GC susceptibility have been reported, but few studies have focused on *DDB1* (*XPE*), *DDB2*, *CSA* and *CSB*.

2.1.1. XPA

The *XPA* gene is located at chromosome 9 (9q22.3) and encodes a zinc finger protein consisting of 273 amino acids [26]. The N terminal domain of XPA is needed for incision activity of the endonucleases involved in NER, and the central DNA-binding domain is the region where damaged DNA binds [27]. Cells or animals deficient for XPA cannot accomplish NER [28].

The literature on the associations between *XPA* polymorphisms and genetic susceptibility of GC has mainly focused on the rs1800975 A/G polymorphism located in the promoter, upstream of the ATG in the 5′ untranslated region (UTR). Dong et al. [29] found in Chinese populations that the (AG + GG) genotype was associated with a reduced risk of GC. However, Palli et al. [30] did not find a significant association of this polymorphism with GC risk, neither in a dominant nor a recessive effect model in an Italian case–control