World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v3.i12.175

World J Gastrointest Oncol 2011 December 15; 3(12): 175-181
ISSN 1948-5204 (online)

REVIEW

Predictive role of *XRCC5*/*XRCC6* genotypes in digestive system cancers

Mei-Due Yang, Chia-Wen Tsai, Wen-Shin Chang, Yung-An Tsou, Cheng-Nan Wu, Da-Tian Bau

Mei-Due Yang, Chia-Wen Tsai, Wen-Shin Chang, Yung-An Tsou, Cheng-Nan Wu, Da-Tian Bau, Terry Fox Cancer Research Laboratory, China Medical University Hospital, 2 Yuh-Der Road, Taichung 40402, Taiwan, China
Chia-Wen Tsai, Wen-Shin Chang, Da-Tian Bau, Graduate Institute of Basic Medical Science, China Medical University, Taichung 40402, Taiwan, China
Cheng-Nan Wu, Department of Medical Laboratory Science and Biotechnology, Central Taiwan University of Science and Technology, Taichung 40601, Taiwan, China
Da-Tian Bau, Graduate Institute of Clinical Medical Science, China Medical University, Taichung 40402, Taiwan, China
Author contributions: All authors contributed to this manuscript.
Correspondence to: Da-Tian Bau, PhD, Professor, Terry Fox Cancer Research Laboratory, China Medical University Hospital, 2 Yuh-Der Road, Taichung 404402, Taiwan, China. datian@mail.cmuh.org.tw
Telephone: +86-42-2052121-1523 Fax: +86-42-2053366
Received: April 22, 2011 Revised: October 6, 2011
Accepted: October 14, 2011
Published online: December 15, 2011

Abstract

Cancers are a worldwide concern; oral, esophageal and gastrointestinal cancers represent important causes of cancer-related mortality and contribute to a significant burden of human health. The DNA repair systems are the genome caretakers, playing a critical role in the initiation and progression of cancers. However, the association between the genomic variations of DNA repair genes and cancer susceptibility is not well understood. This review focuses on the polymorphic genotypes of the non-homologous end-joining DNA repair system, highlighting the role of two genes of this pathway, *XRCC5* and *XRCC6*, in the susceptibility to digestive system cancers and discussing their potential contributions to personalized medicine.

Key words: XRCC5; XRCC6; Polymorphism; Oral cancer; Esophageal cancer; Gastrointestinal cancer; Colorectal cancer

Peer reviewer: Joseph T Tseng, Assistant Professor, Institute of Bioinformatics, College of Bioscience and Biotechnology, National Cheng-Kung University, No.1 University Rd, Tainan 701, Taiwan, China

Yang MD, Tsai CW, Chang WS, Tsou YA, Wu CN, Bau DT. Predictive role of *XRCC5*/*XRCC6* genotypes in digestive system cancers. *World J Gastrointest Oncol* 2011; 3(12): 175-181 Available from: URL: http://www.wjgnet.com/1948-5204/full/v3/i11/175.htm DOI: http://dx.doi.org/10.4251/wjgo.v3.i12.175

INTRODUCTION

The human genome is maintained mainly by DNA repair pathways which can sense all kinds of DNA damage and repair them. In the recent literature, six main DNA repair pathways are identified and studied *via* their individual functional assays: (1) direct reversal repair; (2) nucleotide excision repair; (3) base excision repair; (4)homologous repair (HR); (5) non-homologous end-joining (NHEJ); and (6) mismatch repair. Normally, if these repair pathways fail to repair the DNA damage during the cell cycle arrest caused by DNA abnormality, the cell itself can sense the defects as a "threat" and trigger the cell to undergo apoptosis. However, when the DNA damage is not repaired or turned to the induction of cell apoptosis and terminating the unhealthy cell, the DNA defects will be left and propagated to its offspring cells. Under the latter circumstances, cancer will develop step by step. The decreasing of genomic stability in most cancer types and the identification of cancer predisposition syndromes linked to the defects of DNA repair pathways support the concept that DNA repair genes may play critical roles in opposing cancer initiation and progression[1-3].

One of the most deleterious DNA damaging types is

the double strand break (DSB), which should be repaired in eukaryotes by the two major pathways mentioned above: HR and NHEJ. HR is a template guided, error-free pathway predominantly operating in the S and G2 phases of the cell cycle and involves RAD51, RAD51B/C/D, XRCC2/3, and p53, RPA, BRCA1/2, BLM and MUS81[4]. NHEJ, on the other hand, is a potentially less accurate form of DSB repair, in which the two termini of the broken DNA molecule are processed to form compatible ends that are directly joined. In most cases, NHEJ results in the loss of a few nucleotides at the broken ends, making this pathway error-prone. This article discusses the role of XRCC5/XRCC6 (also known as Ku80/Ku70) hetero-dimers in NHEJ; NHEJ is considered to be the major repair pathway of DSBs in eukaryotic cells during the cell cycle[5]. NHEJ involves the XRCC5/XRCC6, XRCC7 (DNA-dependent protein kinase catalytic subunit; DNA-PKcs), Artemis, XLF, XRCC4, DNA ligase 4, ATM, p53 and MDM2 proteins[6,7]. NHEJ deficiencies can lead to increased genomic instability[8,9] and cause increased tumorigenesis[10-13]. However, the exact roles of these genes and their protein products, such as XRCC5 or XRCC6, in each type of cancer are not well investigated or revealed. The model for DSB repair *via* NHEJ and the proteins involved are shown in Figure 1.

XRCC5 and XRCC6 usually form the heterodimer Ku. They are probably the first proteins that bind to the DNA ends of a DSB and the XRCC5/6-DNA complex recruits and activates XRCC7[14,15]. XRCC5/6 dimer and XRCC7 are proposed to act in the synapsis process[14,15]. *XRCC5* and *XRCC6* knockout mice are growth retarded, radiosensitive and are severely immuno-deficient[16,17]. B-cell development is arrested at an early stage due to a profound deficiency in V(D)J recombination, which is commonly employed by vertebrates to generate diversity as an adaptive immune response[16,17]. Although the XRCC5- or XRCC6-deficient mice are viable, their cells have defects in DNA end joining, which manifest as irradiation sensitivity, growth defects, premature senescence and inability to perform end-joining during V(D)J recombination. All these defects may also happen during human embryonic development. A human cell is statistically insulted by hundreds of thousands exogenous and endogenous DNA damage per day, and if the cell does not repair DSB well, the accumulated genomic instability leads the cell to apoptosis and causes the embryonic lethality of the subject. Therefore, there is no doubt that XRCC5 and XRCC6 are very critical in both genomic stability and human carcinogenesis.

Since the *NHEJ* genes play critical and specific roles during the overall process of repairing the DSBs, if any of them fails to finish its job correctly and immediately, the NHEJ capacity will become lower and the overall genomic instability will become higher. It is therefore tempting to speculate that defects in the NHEJ pathway may be associated with the susceptibility of human cancers. Given this, it is puzzling that no direct genetic evidence has been found to link the defective *NHEJ* genes with cancers. Among them, only mutations in two have been found to predispose carriers to a higher rate of genetic diseases, DNA ligase 4 and Artemis, which are associated with Nijmegen breakage syndrome-like syndrome and severe combined immunodeficiency, respectively[18,19]. One explanation is that any severe defects (null mutants) in NHEJ-related genes would result in great genomic instability and might be incompatible with life, thus no cancer cases can be observed in our population. The crucial and irreplaceable roles of these *NHEJ* gene products may also increase the difficulty of approaching their physiological functions via single gene knockout mice models. For this reason, for these high-penetrance NHEJ genes, only subtle defects arising from low-penetrance alleles (e.g., hypomorphic mutant or polymorphic variant) would escape the cell cycle checkpoint surveillance and allow the cell to survive and to accumulate enough unrepaired genomic alterations required for tumor formation[20,21]. Currently, it is a worldwide trend to approach the subtle variations among subjects by the single nucleotide polymorphism (SNP) technique and investigate their association with human diseases.

The aim of this article is to summarize and evaluate the associations between the SNPs of *XRCC5/XRCC6* genes with the susceptibility to four digestive system cancers, including oral, esophageal, gastric and colorectal cancers. Among the digestive cancers, gastric, liver, and esophageal cancers have continued to be among the top five cancers during the past three decades. More interestingly, colorectal cancer is more and more serious in Asia, especially in China Mainland and Taiwan. However, knowledge about the genomic effects on their incidence, prognosis and responses to chemotherapy or radiotherapy is still lacking. In pancreas cancer, genomic studies are lacking due to the difficulty of collection of enough samples. Although the rapid development of genome-wide association studies and bioinformatics indeed do a great favor in revealing the secret of the human genome in cancer, the knowledge of cancer genomics is still far from satisfying and in need of further studies. Therefore, we hope this article can provide some useful markers in oncology for early detection, prevention and anticancer interventions. To this aim, we have summarized the literature in the second section for oral (2.1), esophageal (2.2), gastric (2.3) and colorectal (2.4) cancers and discussed the contribution of these findings to personalized medicine and therapy in the third section.

XRCC5/*XRCC6* POLYMORPHIC STUDIES IN DIGESTIVE SYSTEM CANCERS

Oral cancer

Oral cancer specifically refers to a subgroup of head and neck malignancies that develop at the lips, tongue, salivary glands, gingiva, mouth floor, oropharynx, buccal surfaces and other intra-oral locations. The World Health Organization has estimated oral cancer to be the eighth most common cancer worldwide. As with other upper aerodigestive tract cancers, five-year survival rates for oral cavity

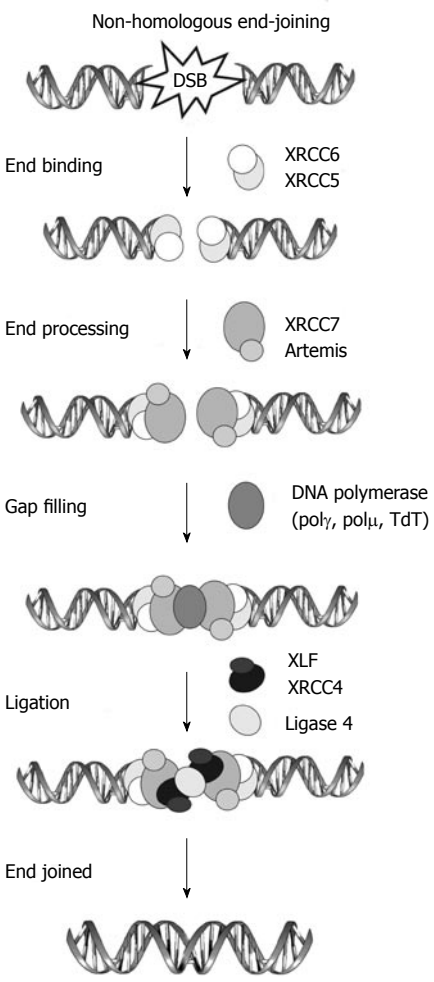

Figure 1 A model for repair of double-strand breaks by non-homologus end-joining.

cancers decrease with delayed diagnosis. Cancers of the oral cavity are thought to progress from premalignant/precancerous lesions, beginning as hyperplastic tissue and developing into invasive squamous cell carcinoma. The most important risk factors for the development of oral cancer in western countries are the consumption of tobacco and alcohol[22,23]. In Asia, chewing betel quid and/or betel nut are responsible for a considerable percentage of oral cancer cases[24,25]. So far, the genomic etiology of oral cancer is of great interest but largely unknown.

In Taiwan, where oral cancer density is the highest in the world, oral cancer is a fatal disease accounting for the fourth highest incidence of malignancy in males and the sixth in females[26]. The relatively high prevalence of oral cancer in Taiwan is mainly because there is a high-risk group of 2.5 million people with the prevalent habits of smoking, alcohol drinking and betel quid chewing. In the literature, there are four papers that investigate the associations of *NHEJ* genes with oral cancer in Taiwan. In 2008, our group found that the C allele of *XRCC6* rs5751129 was a risk marker for oral cancer susceptibility, while those of rs2267437, rs132770 and rs132774 were not[27]. In the next year, we enlarged the investigated population of control/case from 318/318 to 600/600, reporting that *XRCC5* rs828907, but not rs11685387 or rs9288518, was associated with oral cancer susceptibility[28]. People who carried GT and TT genotype at *XRCC5* rs828907 had a 1.6-fold enhanced risk when they also had the habit of betel quid chewing. In addition to *XRCC5* and *XRCC6*, there are two studies that investigated the polymorphic genotypes of *XRCC4* and their association with oral cancer risk in Taiwan[29,30]. These studies reported that the *XRCC4* rs3734091 and rs28360071 genotypes were associated with oral cancer risk. In 2008, a study that investigated Americans with oral premalignant lesions found that there is no association between *XRCC5* rs1051685 genotypes with the susceptibility[31]. The inconsistency can be explained by at least two directions; one, that different populations from different ethnicities were investigated and two, that different SNPs were examined among these studies. The negative findings could not exclude the possibilities that other SNPs of the *XRCC5* may be found to be associated with oral cancer susceptibility. Meanwhile, the positive findings should be verified in an even larger sample size and the functional differences caused by the polymorphic genotypes checked.

Esophageal cancer

Esophageal squamous cell carcinoma (ESCC) is one of the common malignancies with a 5-year survival less than 10%. It is the seventh leading cause of cancer-related deaths in the world[32]. Epidemiologically, it is characterized by a distinctly higher incidence in certain geographical locations, such as China[33]. Smoking tobacco and consuming alcohol are two behavioral factors strongly associated with the risks of both ESCC and esophageal adenocarcinoma[34,35]. ESCC shows a great variation in its geographical distribution and the incidence rates are remarkably higher in distinct high risk areas such as China, Singapore, Iran, France, South Africa, Puerto Rico, Chile, Brazil, northern and eastern Himalayan regions. In 1989, it was thought that the wide geographical variation in the incidence reflects a strong influence of environmental factors[36]. However, recent papers report that the high incidence of ESCC may result primarily from genetic rather than environmental factors which strengthens the importance of continuing to search for the genomic markers for esophageal cancer which are still largely unknown[37-39].

In 2007, Dong and her colleagues recruited 329 esophageal cancer patients and 631 cancer-free controls from China, where esophageal cancer is the fourth leading cause of the cancer death. The risk of esophageal cancer is highly associated with a family history, supporting the concept that genomic effects play an important role in its etiology. Two SNPs of *XRCC5*, C74468A and G74582A (Accession numbers: DQ787434 and DQ787434) were genotyped among the subjects, while no single SNP or combined genotype has been found to be associated with esophageal cancer risk[40]. However, in those subjects with a familial history of esophageal cancer, the C allele of *XRCC5* C74468A seemed to be a protective factor for the incidence[40]. Up to now, there is no report that inves-

tigates the association of *XRCC6* polymorphism with esophageal cancer risk.

Gastric cancer

Gastric cancer is the second most common malignancy and the second most frequent cause of cancer-related death in the world, responsible for approximately 934 000 new diagnoses annually (8.6% of new cancer cases)[41]. Almost two-thirds of cases occurred in Eastern Europe, South America and Asia, with 42% in China alone. In the United States in 2009, an estimated 21 130 new cases (14th most common) of gastric cancer were diagnosed and gastric cancer was responsible for 10 620 deaths (13th most common)[42]. In Europe, gastric cancer ranks as the 5th most prevalent with an estimated 159 900 new cases in 2006 and 118 200 deaths (4th most common cause of cancer-related death)[43].

Now, gastric cancer is still a major health problem worldwide due to its frequency, poor prognosis and limited treatment options. It is often diagnosed in advanced stages and this consequently leads to a poor prognosis. Although the mechanisms of gastric cancer are not yet elucidated, a close relationship between gastric cancer and the provocation, maintenance and modulation of inflammation induced by *Helicobacter pylori* is a well accepted model for gastric carcinogenesis. In addition, high intake of salted, pickled or smoked foods, as well as dried fish and meat and refined carbohydrates significantly increases the risk of developing gastric cancer, while fibers, fresh vegetables and fruit are inversely associated with its risk. However, the genetic factors of gastric cancer are poorly understood.

Dong *et al*[40] found that in those subjects with a familial history of gastric cancer, the C allele of *XRCC5* C74468A seemed to be a protective factor for the incidence. A similar trend was found in the case of esophageal cancer. Also, in those subjects with a familial history of gastric cancer, the A allele of *XRCC5* G74582A seemed to be a protective factor for the incidence, which was not similar to esophageal cancer. Interestingly, as for esophageal and gastric cancer, there is both the similar (C allele of C74468A) and specific (A allele of G74582A) genomic influences from the same *XRCC5* gene. There is no literature investigating and analyzing the association of XRCC6 polymorphism with esophageal cancer risk.

Colorectal cancer

Colorectal cancer is the third most common malignant cancer worldwide. In 2010, an estimated 142 570 new cases of colorectal cancer (CRC) and 21 100 new cases of gastric adenocarcinoma (GA) will be diagnosed in the United States[44]. Noticeably, colorectal cancer remains a significant cause of morbidity and mortality in the United States, Taiwan and throughout the world[45]. Etiological studies have attributed more than 85% of colorectal cancer to environmental factors[46,47] and, in particular, meat consumption, cigarette smoking and exposure to carcinogenic aromatic amines, such as arylamines and heterocyclic amines[48,49]. These carcinogens are thought of as DNA damage inducers responsible for DNA base damage, DNA single-strand breaks and DSBs[50].

In 2009 in Taiwan, where the highest incidence of colorectal cancer is, it was reported that the *XRCC5* rs828907 polymorphism was associated with increased colorectal cancer, while the *XRCC5* rs11685387 and rs9288518 genotypes have no similar association. In people with individual smoking habits, the genomic effect of the *XRCC5* rs828907 on colorectal cancer risk is even more significant with the T allele which can obviously raise the colorectal risk by 2.54-fold. There was no significant joint effect between these genotypes and alcohol drinking on colorectal risk[51]. It is a pity that diet habits, such as meat, vegetable/fruit and fish/shrimp consumption, cannot be clarified due to the incomplete questionnaire information but they have successfully established the relationship between genomic (*XRCC5* genotype) and environmental (smoking habit) factors for colorectal cancer etiology. To date, there is no literature analyzing the association of *XRCC6* polymorphism with colorectal cancer risk or the joint effects of genomic and environmental factors.

CONTRIBUTION OF XRCC5/XRCC6 BIOMARKERS TO PERSONALIZED MEDICINE

In this article, we have reviewed all the associations of *XRCC5* and *XRCC6* genotypes with the susceptibilities for digestive system cancers in the literature, summarizing the highlights of them concisely (Table 1). Generally speaking, individual cancer susceptibility is determined by three groups of factors: lifestyle/environmental factors, genetic/genomic factors and age/gender factors. Among the three, the effects of lifestyle/environmental and age/gender factors may influence somatic cells as genomic and epigenomic damage, which can be altered during the life span. However, the genomic/genetic factors confer a step-by-step but complicated and multi-pathway development of carcinogenesis. Clinical observations suggest that individuals may exhibit dramatic differences in their responses to therapies and drugs and that these variations could be inherited[52,53]. SNPs could serve as not only as the genomic markers, but also the biomarkers in charge of personal cancer susceptibility. These SNPs in the human genome contribute to wide variations in how individuals respond to clinical medications, either by changing the pharmacokinetics (absorption, distribution, metabolism and elimination) of anticancer drugs or by altering the cellular response to therapeutic agents such as radiotherapy.

As shown in Table 1, cancer molecular epidemiologists are devoted to describing subtle differences among subjects in the distribution of genetic SNPs that affect DNA-repair enzymes, drug-metabolizing enzymes, cell-cycle controlling proteins, oncogenes, tumor suppression genes and cellular transporters of cytotoxic chemotherapy to reveal the overview of carcinogenesis. In this re-

Table 1 Summary of the associations for digestive cancers and the polymorphic genotype of XRCC5 and XRCC6 genes

Cancer	Author	Gene	rs number	Location	Study subjects				
					Ethnic area	Cases	Controls	Statistical significance	Brief description
Oral cancer	Hsu[28]	*XRCC5*	828907	Promoter	Taiwan	600	600	S	Allele C is of higher risk
			11685387	Promoter				NS	
			9288518	Intron 19				NS	
	Bau[27]	*XRCC6*	5751129	Promoter	Taiwan	318	318	S	Allele T is of higher risk, and interacted with betel quid chewing habits
			2267437	Promoter				NS	
			132770	Promoter				NS	
			132774	Intron 3				NS	
Esophageal cancer	Dong[40]	*XRCC5*	Accession number: DQ787434[1]	Intron16	China mainland	329	631	S	Allele A is of higher risk
			Accession number: DQ787434[1]	Intron16				NS	
Gastric cancer	Dong[40]	*XRCC5*	Accession number: DQ787434[1]	Intron16	China mainland	255	631	S	Allele A is of higher risk
			Accession number: DQ787434[1]	Intron16				S	Allele G is of higher risk
Colorectal cancer	Yang[51]	*XRCC5*	828907	Promoter	Taiwan mainland	362	362	S	Allele T is of higher risk, and interacted with smoking habits
			11685387	Promoter				NS	
			9288518	Intron 19				NS	

[1]Accession number was provided instead for the rs number is not available. S: Statistically significant; NS: Not statistically significant.

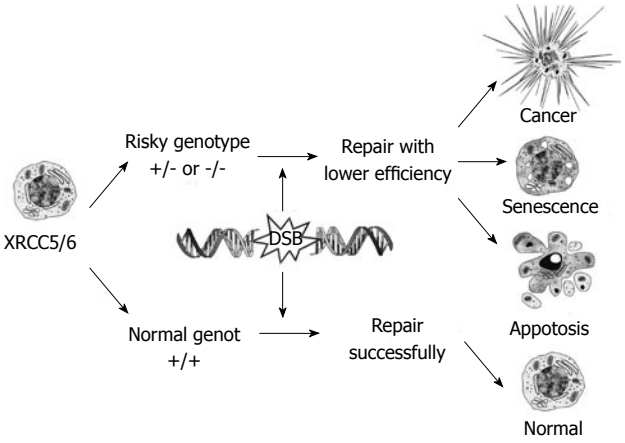

Figure 2 Hypothesis of the XRCC5/XRCC6 genotypic control over the fate of cells.

view, we focus on summarizing the state-of-the-art studies of *XRCC5* and *XRCC6* genes, which are upstream and specifically critical in NHEJ, and their contribution to digestive system cancers. Although currently the hypothesis-free genome-wide association studies (GWAS) are largely applied to studies including cancer research, knowledge about the associations of specific genotypes with specific cancers is still limited and in urgent need. The contributions of the SNPs listed here in Table 1 to other human cancers and cancer-related diseases, and their functional biological meanings to carcinogenesis, all need further investigations. Meanwhile, they may serve as candidate targets pharmacogenomically for the development of personalized anticancer drugs. The hypothesis of how the *XRCC5/XRCC6* genotypes control the fate of cells after DSB insults is shown in Figure 2.

Some DNA repair genes in the DNA repair pathways, such as *XRCC4* in NHEJ[54], *MGMT* in direct removal pathway[55,56], *XRCC1* in base excision repair[57], *ERCC1* and *ERCC2* in NER[58,59], *hMSH2* in mismatch repair[57] and *hHR21* in HR[58], are all thought to be anticancer candidate targets. From now on, *XRCC5/XRCC6* may be added to the list above. It should be also noted that anticancer drugs may induce DSBs itself in the feasibility of chemotherapy. On the other hand, co-treatments of DNA-damaging agents and radiation have a central role besides other cancer treatment modalities. The balance between DNA damage and capacity of DNA repair mechanisms determines the final therapeutic outcome. The capacity of cancer cells to complete DNA repair mechanisms is important for therapeutic resistance and has a negative impact upon therapeutic efficacy. Pharmacological inhibition of recently detected targets of DNA repair with several small-molecule compounds, therefore, has the potential to enhance the cytotoxicity of anticancer agents. Futami and his colleagues also discovered that inhibition of the expression of various genes associated with chromosome stabilization induces cancer cell-specific apoptosis and inhibits cell proliferation[60].

In this article, most of the studies are case-control investigations in one or two ethnic groups. The inconsistency of choosing the SNPs and the insufficient sample size limits the multiple comparisons of human populations around the world. Further incorporations among populations and integrations of genotype-phenotype relationship analysis, population-based tissue and blood functional measurements, clinical outcome records, especially those in chemo- and radiotherapy responses, are

in urgent need for international studies on inter-ethnic variations, using these pharmacogenomic biomarkers. The integration of pharmacogenomic, phenotypic and pathological biomarkers, is the main stream in the development of cancer risk prediction, personalized medicine and therapy evaluation.

REFERENCES

1 **Hakem R**. DNA-damage repair; the good, the bad, and the ugly. *EMBO J* 2008; **27**: 589-605
2 **Spry M**, Scott T, Pierce H, D'Orazio JA. DNA repair pathways and hereditary cancer susceptibility syndromes. *Front Biosci* 2007; **12**: 4191-4207
3 **Berwick M**, Vineis P. Markers of DNA repair and susceptibility to cancer in humans: an epidemiologic review. *J Natl Cancer Inst* 2000; **92**: 874-897
4 **Valerie K**, Povirk LF. Regulation and mechanisms of mammalian double-strand break repair. *Oncogene* 2003; **22**: 5792-5812
5 **Pfeiffer P**, Goedecke W, Kuhfittig-Kulle S, Obe G. Pathways of DNA double-strand break repair and their impact on the prevention and formation of chromosomal aberrations. *Cytogenet Genome Res* 2004; **104**: 7-13
6 **Bassing CH**, Chua KF, Sekiguchi J, Suh H, Whitlow SR, Fleming JC, Monroe BC, Ciccone DN, Yan C, Vlasakova K, Livingston DM, Ferguson DO, Scully R, Alt FW. Increased ionizing radiation sensitivity and genomic instability in the absence of histone H2AX. *Proc Natl Acad Sci USA* 2002; **99**: 8173-8178
7 **Shrivastav M**, De Haro LP, Nickoloff JA. Regulation of DNA double-strand break repair pathway choice. *Cell Res* 2008; **18**: 134-147
8 **Gilley D**, Tanaka H, Hande MP, Kurimasa A, Li GC, Oshimura M, Chen DJ. DNA-PKcs is critical for telomere capping. *Proc Natl Acad Sci USA* 2001; **98**: 15084-15088
9 **Goytisolo FA**, Samper E, Edmonson S, Taccioli GE, Blasco MA. The absence of the dna-dependent protein kinase catalytic subunit in mice results in anaphase bridges and in increased telomeric fusions with normal telomere length and G-strand overhang. *Mol Cell Biol* 2001; **21**: 3642-3651
10 **Difilippantonio MJ**, Zhu J, Chen HT, Meffre E, Nussenzweig MC, Max EE, Ried T, Nussenzweig A. DNA repair protein Ku80 suppresses chromosomal aberrations and malignant transformation. *Nature* 2000; **404**: 510-514
11 **Ferguson DO**, Alt FW. DNA double strand break repair and chromosomal translocation: lessons from animal models. *Oncogene* 2001; **20**: 5572-5579
12 **Gao Y**, Ferguson DO, Xie W, Manis JP, Sekiguchi J, Frank KM, Chaudhuri J, Horner J, DePinho RA, Alt FW. Interplay of p53 and DNA-repair protein XRCC4 in tumorigenesis, genomic stability and development. *Nature* 2000; **404**: 897-900
13 **Zhu C**, Mills KD, Ferguson DO, Lee C, Manis J, Fleming J, Gao Y, Morton CC, Alt FW. Unrepaired DNA breaks in p53-deficient cells lead to oncogenic gene amplification subsequent to translocations. *Cell* 2002; **109**: 811-821
14 **Lieber MR**. The mechanism of human nonhomologous DNA end joining. *J Biol Chem* 2008; **283**: 1-5
15 **Lieber MR**, Ma Y, Pannicke U, Schwarz K. Mechanism and regulation of human non-homologous DNA end-joining. *Nat Rev Mol Cell Biol* 2003; **4**: 712-720
16 **Gu Y**, Seidl KJ, Rathbun GA, Zhu C, Manis JP, van der Stoep N, Davidson L, Cheng HL, Sekiguchi JM, Frank K, Stanhope-Baker P, Schlissel MS, Roth DB, Alt FW. Growth retardation and leaky SCID phenotype of Ku70-deficient mice. *Immunity* 1997; **7**: 653-665
17 **Nussenzweig A**, Chen C, da Costa Soares V, Sanchez M, Sokol K, Nussenzweig MC, Li GC. Requirement for Ku80 in growth and immunoglobulin V(D)J recombination. *Nature* 1996; **382**: 551-555
18 **Li L**, Moshous D, Zhou Y, Wang J, Xie G, Salido E, Hu D, de Villartay JP, Cowan MJ. A founder mutation in Artemis, an SNM1-like protein, causes SCID in Athabascan-speaking Native Americans. *J Immunol* 2002; **168**: 6323-6329
19 **O'Driscoll M**, Cerosaletti KM, Girard PM, Dai Y, Stumm M, Kysela B, Hirsch B, Gennery A, Palmer SE, Seidel J, Gatti RA, Varon R, Oettinger MA, Neitzel H, Jeggo PA, Concannon P. DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. *Mol Cell* 2001; **8**: 1175-1185
20 **Bau DT**, Mau YC, Ding SL, Wu PE, Shen CY. DNA double-strand break repair capacity and risk of breast cancer. *Carcinogenesis* 2007; **28**: 1726-1730
21 **Fu YP**, Yu JC, Cheng TC, Lou MA, Hsu GC, Wu CY, Chen ST, Wu HS, Wu PE, Shen CY. Breast cancer risk associated with genotypic polymorphism of the nonhomologous end-joining genes: a multigenic study on cancer susceptibility. *Cancer Res* 2003; **63**: 2440-2446
22 **Ogden GR**. Alcohol and oral cancer. *Alcohol* 2005; **35**: 169-173
23 **Warnakulasuriya S**, Sutherland G, Scully C. Tobacco, oral cancer, and treatment of dependence. *Oral Oncol* 2005; **41**: 244-260
24 **Gupta PC**, Ray CS. Smokeless tobacco and health in India and South Asia. *Respirology* 2003; **8**: 419-431
25 **Nair U**, Bartsch H, Nair J. Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. *Mutagenesis* 2004; **19**: 251-262
26 **Department of Health, Taiwan.** Cancer registration system annual report. Taiwan: Department of Health, 2009
27 **Bau DT**, Tseng HC, Wang CH, Chiu CF, Hua CH, Wu CN, Liang SY, Wang CL, Tsai CW, Tsai MH. Oral cancer and genetic polymorphism of DNA double strand break gene Ku70 in Taiwan. *Oral Oncol* 2008; **44**: 1047-1051
28 **Hsu CF**, Tseng HC, Chiu CF, Liang SY, Tsai CW, Tsai MH, Bau DT. Association between DNA double strand break gene Ku80 polymorphisms and oral cancer susceptibility. *Oral Oncol* 2009; **45**: 789-793
29 **Chiu CF**, Tsai MH, Tseng HC, Wang CL, Wang CH, Wu CN, Lin CC, Bau DT. A novel single nucleotide polymorphism in XRCC4 gene is associated with oral cancer susceptibility in Taiwanese patients. *Oral Oncol* 2008; **44**: 898-902
30 **Tseng HC**, Tsai MH, Chiu CF, Wang CH, Chang NW, Huang CY, Tsai CW, Liang SY, Wang CL, Bau DT. Association of XRCC4 codon 247 polymorphism with oral cancer susceptibility in Taiwan. *Anticancer Res* 2008; **28**: 1687-1691
31 **Yang H**, Lippman SM, Huang M, Jack Lee J, Wang W, Spitz MR, Wu X. Genetic polymorphisms in double-strand break DNA repair genes associated with risk of oral premalignant lesions. *Eur J Cancer* 2008; **44**: 1603-1611
32 **Ando N**, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg* 2000; **232**: 225-232
33 **Zhang H**, Chen Z, Cheng J, Zhu X, Guo W, Hu A, Du Y, Zhou Y, Wang Y. The high incidence of esophageal cancer in parts of China may result primarily from genetic rather than environmental factors. *Dis Esophagus* 2010; **23**: 392-397
34 **Navarro Silvera SA**, Mayne ST, Risch HA, Gammon MD, Vaughan T, Chow WH, Dubin JA, Dubrow R, Schoenberg J, Stanford JL, West AB, Rotterdam H, Blot WJ. Principal component analysis of dietary and lifestyle patterns in relation to risk of subtypes of esophageal and gastric cancer. *Ann Epidemiol* 2011; **21**: 543-550
35 **Kamangar F**, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. *Gastroenterol Clin North Am* 2009; **38**: 27-57, vii
36 **Siddiqi M**, Preussmann R. Esophageal cancer in Kashmir--an assessment. *J Cancer Res Clin Oncol* 1989; **115**: 111-117
37 **Hussain S**, M Y, Thakur N, Salam I, Singh N, Mir MM, Bhat

MA, Siddiqi MA, Das BC, Bharadwaj M. Association of cyclin D1 gene polymorphisms with risk of esophageal squamous cell carcinoma in Kashmir Valley: a high risk area. *Mol Carcinog* 2011; **50**: 487-498
38 **Lv J,** Cao XF, Ji L, Zhu B, Wang DD, Tao L, Li SQ. Association of β-catenin, Wnt1, Smad4, Hoxa9, and Bmi-1 with the prognosis of esophageal squamous cell carcinoma. *Med Oncol* 2011; Epub ahead of print
39 **Huang CG**, Iv GD, Liu T, Liu Q, Feng JG, Lu XM. Polymorphisms of COMT and XPD and risk of esophageal squamous cell carcinoma in a population of Yili Prefecture, in Xinjiang, China. *Biomarkers* 2011; **16**: 37-41
40 **Dong XJ**, Wang N, Guo W, Zhou RM, Zhang XJ, Li Y. [Correlations of XRCC5 polymorphisms to genetic susceptibility to esophageal squamous cell carcinoma and gastric cardiac adenocarcinoma in a high incidence region]. *Ai Zheng* 2007; **26**: 280-284
41 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108
42 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249
43 **Jackson C**, Cunningham D, Oliveira J. Gastric cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009; **20** Suppl 4: 34-36
44 **Jemal A**, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277-300
45 **Gellad ZF**, Provenzale D. Colorectal cancer: national and international perspective on the burden of disease and public health impact. *Gastroenterology* 2010; **138**: 2177-2190
46 **Doll R**, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 1981; **66**: 1191-1308
47 **Thomas HJ**. Familial colorectal cancer. *BMJ* 1993; **307**: 277-278
48 **Giovannucci E**, Colditz GA, Stampfer MJ, Hunter D, Rosner BA, Willett WC, Speizer FE. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. *J Natl Cancer Inst* 1994; **86**: 192-199
49 **Heineman EF**, Zahm SH, McLaughlin JK, Vaught JB. Increased risk of colorectal cancer among smokers: results of a 26-year follow-up of US veterans and a review. *Int J Cancer* 1994; **59**: 728-738
50 **Pryor WA**, Hales BJ, Premovic PI, Church DF. The radicals in cigarette tar: their nature and suggested physiological implications. *Science* 1983; **220**: 425-427
51 **Yang MD**, Hsu YM, Kuo YS, Chen HS, Chang CL, Wu CN, Chang CH, Liao YM, Wang HC, Wang MF, Bau DT. Significant association of Ku80 single nucleotide polymorphisms with colorectal cancer susceptibility in Central Taiwan. *Anticancer Res* 2009; **29**: 2239-2242
52 **Evans WE**, McLeod HL. Pharmacogenomics--drug disposition, drug targets, and side effects. *N Engl J Med* 2003; **348**: 538-549
53 **Kawai Y**, Kikuchi T, Mitani Y, Kogo Y, Itoh M, Usui K, Kanamori H, Kaiho A, Takakura H, Hoshi K, Cizdziel PE, Hayashizaki Y. Sensitive detection of EGFR mutations using a competitive probe to suppress background in the SMart Amplification Process. *Biologicals* 2008; **36**: 234-238
54 **Wu CN**, Liang SY, Tsai CW, Bau DT. The role of XRCC4 in carcinogenesis and anticancer drug discovery. *Recent Pat Anticancer Drug Discov* 2008; **3**: 209-219
55 **Dolan ME**, Moschel RC, Pegg AE. Depletion of mammalian O6-alkylguanine-DNA alkyltransferase activity by O6-benzylguanine provides a means to evaluate the role of this protein in protection against carcinogenic and therapeutic alkylating agents. *Proc Natl Acad Sci USA* 1990; **87**: 5368-5372
56 **Kaina B**, Mühlhausen U, Piee-Staffa A, Christmann M, Garcia Boy R, Rösch F, Schirrmacher R. Inhibition of O6-methylguanine-DNA methyltransferase by glucose-conjugated inhibitors: comparison with nonconjugated inhibitors and effect on fotemustine and temozolomide-induced cell death. *J Pharmacol Exp Ther* 2004; **311**: 585-593
57 **Andreassen CN**, Alsner J, Overgaard M, Overgaard J. Prediction of normal tissue radiosensitivity from polymorphisms in candidate genes. *Radiother Oncol* 2003; **69**: 127-135
58 **Isla D**, Sarries C, Rosell R, Alonso G, Domine M, Taron M, Lopez-Vivanco G, Camps C, Botia M, Nuñez L, Sanchez-Ronco M, Sanchez JJ, Lopez-Brea M, Barneto I, Paredes A, Medina B, Artal A, Lianes P. Single nucleotide polymorphisms and outcome in docetaxel-cisplatin-treated advanced non-small-cell lung cancer. *Ann Oncol* 2004; **15**: 1194-1203
59 **Ryu JS**, Hong YC, Han HS, Lee JE, Kim S, Park YM, Kim YC, Hwang TS. Association between polymorphisms of ERCC1 and XPD and survival in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy. *Lung Cancer* 2004; **44**: 311-316
60 **Futami K**, Takagi M, Shimamoto A, Sugimoto M, Furuichi Y. Increased chemotherapeutic activity of camptothecin in cancer cells by siRNA-induced silencing of WRN helicase. *Biol Pharm Bull* 2007; **30**: 1958-1961

S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Xiong L