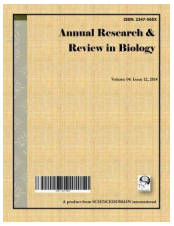

Annual Research & Review in Biology

24(6): 1-12, 2018; Article no.ARRB.39614
ISSN: 2347-565X, NLM ID: 101632869

The Role of TNF-Alpha, Beta, XRCC1 and p53 Gene Predisposition in Cancers

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Authors' contributions

This work was carried out in collaboration between both authors. Author SK designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript. Author GS managed the analyses of the study. Both the authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ARRB/2018/39614
Editor(s):
(1) J. David Puett, Professor, Department of Biochemistry and Molecular Biology, University of Georgia, Athens, USA.
(2) George Perry, Dean and Professor of Biology, University of Texas at San Antonio, USA.
Reviewers:
(1) Lawrence M. Agius, University of Malta, Malta.
(2) Tabe Franklin Nyenty, University of Ngaoundere, Cameroon.
(3) Bensu Karahalil, Gazi University, Turkey.
Complete Peer review History: http://www.sciencedomain.org/review-history/23592

Review Article

Received 8th December 2017
Accepted 26th February 2018
Published 12th March 2018

ABSTRACT

Cancer is a group of diseases characterized by abnormal and uncontrolled cellular growth and differentiation. The major cause of Cancer consists of different types of genetic alterations that include gene substitutions, point mutations and gene amplification leading to damage in molecular pathways responsible for cell growth, survival, and metastasis. These changes develop in the majority of cases with a specific type of tumor. Genes can be used as biomarkers for identification and development of targeted treatments and also for predicting various responses to therapies. The aim of the present review is to reveal the role of tumorigenesis in TNF alpha, beta, xrcc1 and p53 genes in cancer susceptibility to gene predisposition.

Keywords: Tumorigenesis; tumor necrosis factor; XRCC1; p53; predisposition; SNPs.

1. INTRODUCTION

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Cancer is a group of deadly diseases it is characterized by abnormal and uncontrolled cellular growth and differentiation. Multiple genic expression confers a survival advantage and unlimited proliferative potential to somatic or ger m cells. Complex relations like genetical and environmental factors cause cancer to any part of the body due to damage to DNA. Novel techniques in biomedical research make an easy way to identify several genes as biomarkers of cancers for the identification, screening, diagnosi s, and treatment. Another use of biomarkers is to find the early perception of cancer, design spo radic therapies for the diseases including signalin g molecules associated with cellular developmen t, metabolism, and apoptosis, inculcating to obse rve the functional damage with molecular and cellular obstructions. Major exposition of genetic alterations exhibited in three classes of genes proto-oncogenes, tumor suppressor genes, and DNA repair genes grouping together for the contribution of the development of cancer genotypically and phenotypically. These genetic alterations include gene substitutions, point mutations and gene amplifications that lead to damage in molecular pathways responsible for cell growth, survival, and metastasis. When such changes develop in the majority of cases with a specific type of tumor, genes can be used as biomarkers for identification and development of targeted treatments besides predicting gene responses to various therapies [1]. The present review showed the role of tumorigenesis in TNF alpha, beta, xrcc1 and p53 genes with cancer susceptibility and genic predisposition.

2. PRO-TUMORIGENIC-TUMOR NECRO-SIS FACTOR-ALPHA (TNF- α)

The central premise of this review article correctly identifies as the axial involvement of inflammation and chronic inflammation in carcinogenesis. Chronic inflammatory mediators exhibit multiple effects in the development of tumors, the growth of the tumor depends on intrinsic and extrinsic pathways of inflammation. On the other hand, inflammation highly supports carcinogens, malignant formation, tumor growth invasion, and metastasis**.** Among all other Cancers, the 20% of cancers are combined with chronic inflammation and most of it contains solid tumors with inflammatory infiltrates. Tumor initiation, growth, and progression of many immune cell effects are mediated by pro-inflammatory cytokines. The established pro-tumorigenic cytokine is a tumor necrosis factor alpha (TNF- α**)**. Tumorigenesis modifies these cytokines as attractive targets for accurate treatment of cancer. The TNF**-**α gene acts as master regulator gene of tumor-associated inflammation and defense against infection. This cytokine is involved in multiple inflammatory and immune responses and plays role in the pathogenesis of many autoimmune and infectious diseases. TNF- α is also called TNF, cachexin, or cachectin, it regulates the transcription levels [2,3]. The human TNF gene (TNF-α) was discovered in 1985 [4]. It is situated on chromosome 6p21, contains 4 exons. The last exon consists of more than 80% of the secreted protein [5]. TNF actively binds two receptors, TNFR1 and TNFR2. TNFR1 is expressed in many tissues, and totally operate the membrane-bound and soluble trimeric forms of TNF, and the other hand TNFR2 is observed in the immune cellular system and respond to the membrane-bound form of the TNF homotrimer. The death domain of TNFR-1 indicates the capacity of inducing apoptotic cell death, the major differences between these two receptors are the absence of death domain in TNFR2 [6].

The process of growth stimulating, inhibitory and self-regulatory properties of the body organs are influenced by TNF-α. The functional role of TNF-α is to control the immune cells, inflammation, represses tumorigenesis, viral replication and responds to Interleukin 1 and Interleukin 6 producing cells and TNF- α also declined to regulate their production leading to a variety of human cancers [7] and inflammatory bowel disease (IBD) [8]. TNF-α promotes chronic impacts along with acute pathological regulations, causes necrosis of some types of tumors. It stimulates the growth of other types of tumor cells. The increasing levels of TNF- α correlate with high risk of mortality [9]. TNF- α is involved in inflammatory disorders of inflammatory and non-inflammatory origin [10]. The storage of TNF- α in the body for a long time loses its antitumor activity with polymerization of the cytokine due to the shedding of TNF receptors by tumor cells. However, large production of anti-TNF antibodies is found in patients with carcinomas or chronic infection. It also leads to disruptions in the alpha-2 macroglobulin proteinase system cytokine deregulation. Continuous overproduction of TNF- α leads to a condition called as cachexin, characterized by anorexia, catabolism, weight loss and anemia and this large production of TNF-α occurs in the illness of cancer.

3. TNF- α ROLE IN DIFFERENT CANCERS

The polymorphism at -308 positions in G to A transition of the TNF-α gene is located within the binding site of the AP-2 repressive transcription factor. The less common allele A2 (-308A) results from a lack of AP-2 binding and, leads to increased TNF-α gene expression [11]. The A2 allele is correlated with some malignancies like breast, gastric cancer and possibly with thrombosis [12,13]. Microsatellite polymorphisms situated in the TNF-α locus reports association in increased risk of gastric and colorectal cancer [14]. Elevated levels of serum with TNF-α protein was observed in European patients with oral cancer, but no association was found in Taiwanese patients [15,16]. Several reports indicated that serum concentrations with TNF are increased in various cancer patients [17,18]. TNF expression levels also higher in different pre-neoplastic and tumor tissues [17-19] and the increased TNF expression levels associated with the susceptibility of malignant diseases like prostate cancer, breast cancer, and cervical carcinoma, chronic lymphocytic leukemia, Barrett's adenocarcinoma [17,18,20] colorectal neoplasia [21]. The decreased levels of serum TNF concentration was observed in breast and prostate cancer patients at the time of chemotherapy treatment [22]. These findings showed that TNF involved in a major tumor progression and it is considered as a prime risk of prognosis for cancer patients. Single nucleotide polymorphisms (SNPs) at position −308 in the TNF promoter (−308G/A) is found to be predisposed to various types of cancer. The person carrying higher TNF expression levels with TNF-308G/A had an increased cancer risk, mainly invasive cervical cancer [23], gastric cancer [24], non-Hodgkin's lymphoma [25,26], ulcerative colitis-associated colorectal cancer [27], hepatocellular carcinoma [28], and non-small cell lung cancer [29]. A study performed in a north European population, showed significance with the vascular invasion of breast cancer [30] and the results suggest that the −308A allele promotes and associates with cancer development and progression. Another study mentioned that the −238A allele in the TNF-promoter has decreased susceptibility to lung cancer, gastric cancer, uterine cervical cancer, colorectal cancer, or renal cell carcinoma [31]. The TNF-857T allele increases the risk of B-cell lymphoma [32]. These reports indicated that TNF has a tumor-promoting character and TNF promoter SNPs are the major associates of cancer risk. Nowadays TNF is used in cancer treatment in the isolated limb perfusion (ILP) adjustment of soft tissue sarcoma (STS), and metastases confined to the limb [33].

4. TUMOR NECROSIS FACTOR BETA (TNF-β)

TNF- β also known as Lymphotoxin- α is belonging to a major histocompatibility complex-related with TNF family. It is obtained from the Th1 type T-cells and promotes vascular endothelial cells to modify their surface adhesion molecules to bind the phagocytic cells. It is a potent multifunctional cytokine regulates T and B lymphocytes. The functional activities are similar to TNF-α, but TNF-β is most important for the origin of lymphoid organs. These cytokines provide essential coordinated pathways which lead to communication for inflammatory and immune responses. Reactions from the specific cellular receptors, these cytokines act as a signaling pathway caused by cell death, survival, and differentiation. The Lymphotoxin also consists of similar activities like TNF produced by lymphocytes, other than macrophages or neutrophils. The protein consists of a specific potent cytotoxic activity on tumor cells with multiple target cells. The recombinant TNF-beta contains a 171 amino acid fragment, for the mature TNF-beta chain protein and is elevated in E. coli combined with amino-terminal hexahistidine tag [34,35]. The protein binds the lymphotoxin-alpha and lymphotoxin-beta. The encoded protein-ligand plays a role in the growth and operation of lymphoid tissue and transformed cells. The Function of the encoded protein leads to apoptosis and release of the cytokine interleukin 8.

5. TNF – β ROLE IN DIFFERENT CANCERS

The first intron of the TNF – β gene with G/A polymorphism located at position 252, showed elevated expressions in the concentration of TNF-α and TNF-β proteins in plasma [36,37]. Increasing levels of TNF-β expressions of the mRNA and the protein levels were also exhibited with the correlation of the less common allele B1 (252G) [36]. The TNF-β (G252A) polymorphism is also associated with increased risk of development in a breast, esophageal, gastric and colorectal cancer [38]. A study reveals that the allele frequency of the B1 homozygotes is higher than 16% in Europeans and 13% in Asians [38]. The combinational effects of TNF-α and TNF-β polymorphisms were obtained in patients with breast or esophageal cancer, the genotypes

exhibited significant overexpression levels and associated with an increased risk of cancer development [38]. TNF-β with high expression of B1 allele was also observed with a significantly increased risk in patients with osteosarcoma, breast, colorectal and bladder cancer [39]. The TNF-α and TNF-β genotypes together detected in a high ratio of genotypes with A2A2/B1B1, A1A2/B1B2, and A1A2/B1B1, it indicates that the TNF-α gene, TNF-β also plays an important role in the significant risk of oral cancer, though B1 increases TNF-β production [40]. The genotypes of A1A2/B1B2 reported a low risk of oesophageal and gastric cancer in Chinese, and the major risk of myeloma in English Caucasians [41].

6. DNA REPAIR GENES-XRCC1

The responsibilities of Genomic stability and integrity are maintaining the exact DNA replication. DNA repair systems play a major role in regulating the human genome integrity. Loss of ability in the repair capacity due to either mutations or inherited polymorphisms in DNA repair genes leads to differentiation of the DNA repair ability. Modifications in DNA repair genes are associated with various cancers [42]. A cell that has obtained a large amount of DNA damage and no longer capacity to repair damage incurred to its DNA, leads to one of the three possible states including an irreversible state of dormancy, and cell suicide or apoptosis or programmed cell death, unregulated cell division, which can form cancerous tumors. DNA repair systems are accumulating several multienzymes, multistep processes, are fundamental to the controlling of genomic stability and integrity in the replication errors, environmental depreciation and the cumulative changes of aging. The DNA-repair enzymes influence the DNA adducts levels through genetic polymorphisms [43]. DNA repair capacity may increase the risk of the disease. Most of the DNA repair genes, X-ray repair cross-complementing group1 (XRCC1) associations elevated in various cancers like breast [42] lung [44], head and neck [45] Bladder cancer [46] Squamous cell carcinoma of head and neck [47], and XRCC1 is a protein present in humans and it is a major gene involved in DNA repair. It is located on chromosome 19q13, involving17 exons and encodes 633 amino acids. It is important for mammalian viability with efficient repair of single-strand breaks and damaged bases in DNA [48]. The major function of XRCC1 is a modulator of the multiple activities involved in base excision repair in mammalian cells through interacting with and combining together of DNA polymerase β, DNA ligase III and forms a repair complex [49] and poly (ADP-ribose) polymerase in the N-terminal, C terminal and central regions of XRCC1 gene. This pathway repairs the damaged DNA caused by a different variety of endogenous and exogenous factors involving oxidation, alkylating agents and ionizing radiation [50].

This protein binds directly to nicked DNA, the association of gapped DNA with DNA polymerase Beta, resulting from protein directly involved in independent DNA damage recognition [51]. Although mutations in XRCC1 have been showed to disrupt the protein function by modifying binding sites or catalytic domain of the protein [52].The deficiency of XRCC1 causes reduced a capacity of genetic stability and increases the spontaneous or induced chromosome translocations and deletions [53]. Base excision DNA repair (BER) is one of the major proactive DNA repair pathways for important cellular defense mechanism against the harmful effects of the regularly damaged or improper bases in DNA [54]. DNA repair enzymes regulate the DNA to repair the damaged nucleotide residues formed by replication or carcinogen exposures and compounds of cytotoxic mutations in carcinogenesis [55]. Major damage to DNA and its repair is a cause for various types of cancer [56-59]. Lack of DNA repair efficiency leads to mutations in genes, because of the functional loss of the DNA repair protein. Several mutations and polymorphisms are expressed in the number of genes encoding for DNA repair enzymes. DNA damage is a form of cell stress and injury that has been involved in many cancers. The relation between oxidative induced stress and different cellular defense mechanisms leads to oxidative injury. Sometimes oxidative stress results in DNA or protein damage leading to cell suicide (apoptosis). Cell injuries and cell stress are repaired by antioxidant enzymes and DNA repair mechanisms.

7. XRCC1 ROLE IN DIFFERENT CANCERS

The studies suggested that the XRCC1 gene having 300 SNPs, the extensively studied SNPs are XRCC1 Arg194Trp and XRCC1 Arg399Gln [60]. Many studies have indicated that the XRCC1 Arg194Trp polymorphism increases the development of different kinds of cancers like glioma and thyroid cancer, but several meta-

analyses revealed that no correlation between XRCC1 Arg194Trp polymorphism and risk of head and neck cancer, hepatocellular carcinoma, lung cancer [61] on the other hand XRCC1 399Gln allele showed with multiple DNA damages in phenotypes of human cells and tissues in different types of cancers. The variant 399A allele was correlated with an increased risk of stomach cancer [62,63] lung [64,65] prostate cancer [66] and moreover, this allele has shown a decreased risk of esophageal cancer and bladder [67]. A study indicates that the 194 Arg/Arg genotype is associated cancer risk factor for oral cavity and pharynx [68]. There was a study of differences observed in NNK induced sister chromatid exchange between cells with the codon 194 Arg/Arg genotype and codon 194 Arg/Trp genotype in different types of cancers [69]. A hypothetical analysis reveals that the *XRCC1-399* Gln allele is correlated with elevated risk of smoking-dependent cancers including a major risk of lung cancer [70], moreover inconsistent reports also exist [71,72]. In the case of Breast cancer, the *XRCC1-399* Gln allele was associated significantly in non-smokers with detectable PAH-adducts [73].

8. TUMOR SUPPRESSOR GENES p53

The gardener gene of the genome p53 is located on chromosome 17p13 and is the single most common target for genetic variations in human tumors. An oncoprotein MDM2 with over-amplification showed in sarcomas are reported to be associated with p53 [74]. Two different mechanisms are involved in tumor formation. In the first, p53 stimulates the phosphatase 21 cyclin-dependent kinase inhibitor gene in response to DNA damage. Secondly, the loss of p53 gene in cells avoids the p21 gene transcription to the increased expression of the multiple Cdks normally turned off p21, results from cellular multiplication. P53 restraints are involved in inducing apoptosis. Activation of the p53 transcriptional factor responses starts with cellular signaling which mainly causes DNA damage. Inactive p53 and MDM2 triggers post-translational modification, apoptosis lead to altering the cell cycle through p21 and triggering the caspase cascade reactions [75]. Phosphorylation of p53 damages the ability of MDM2 to inhibit p53-dependent transactivation, mostly due to alteration of p53 [76]. Dephosphorylation of p53 enhances the ability at a consensus binding site for DNA [77]. Mutation in the arginine residue abolishes transport of p53 to the nucleus. The nuclear protein p53 binds to single, double-stranded DNA non-specifically, along with that the mutant p53 showed the high affinity towards single-stranded DNA compared with the double-stranded DNA [78]. The pleiotropic effects of p 53 act as transcription-dependent and transcription-independent mechanism. p53 activation leads to homotetramerization with its functions of transcriptional activations also induced by transactivating target genes in intransient cell cycle arrest at G1 or G2 phase [79]. Cell cycle checkpoint arrest mainly in the stress conditions, inhibiting the accumulation of genetic errors p53 can also take action in permanent arrest, or senescence, with the help of transactivation genes like *p21CIP1/WAF1* [80]. Worldwide genome studies revealed that mutant p53 are dynamic of modulating the expression of transcripts. p53 acts as a transcription factor capable of on and off mechanism of genes in response to different gene expressions [81].

The P53 gene is a transactivation domain. The wild-type p53 gene is able to be down-regulated and amplificated with proliferating cell nuclear antigen (PCNA) and can interfere with the induction of c-fos mRNA during serum stimulation [82]. The decreasing levels of p53 are observed in normal cells, but the overexpression in many tumors of different sites proposed that p53 may be a transformation-related antigen [83]. The ability of the wild-type p53 to suppress the transformation of cells in culture by other oncogenes by the growth of transformed cells in culture [84,85], the tumor formation in animals and humans is mainly due to deletions or point mutations of the wild-type p53 allele [86-88]. P53 oncogene functionally blocks the interaction of DNA polymerase viral replication like SV40 [89], and it may bind to an analogous cellular replication protein to prevent entry into S phase [90]. The p53 gene plays a critical role in cell cycle regulation and induction of apoptosis, DNA repair, and genomic instability, all of which are central to the prevention of human cancer forming agents. Inactivation of the wild-type p53 function is frequently seen during the development of cancer. Inactivation of p53 results mutation, inhibition, nuclear DNA damage, degradation protein levels through the MDM2 and aberrant transcription. The p53 tumor suppressor gene mutations associated with over 50% of all human tumors [91]. Regulations of the cell cycle arrest by the activation of p53 protein alterations due to mutations provide evidence for clonal expansion of neoplastic cells [92]. Failure of the tumor

suppressor responses, inactive p53 also incapable to activate expression of MDM2.These p53 mutant proteins are profusely unstable and accumulate in high levels in the tumor cells [93]. Functional p53 may also be inactivated through over expression of the mdm2 gene in some tumors, especially sarcomas since the MDM2 protein speedy degrades and inhibits p53 by binding to the protein [94]. p53 tumor suppressor gene essential for the DNA damage checkpoint, but it was simultaneously observed to have a larger function after cellular stress, such as oncogenes activation or hypoxia [95]. The p53 protein functions as a tetrameric transcription factor found at very low levels in normal unstressed cells. The most common genetic alterations noticed in human cancers with p53 gene mutations [96]. p53 also plays a major role in multiple DNA repair pathways including Wild-type p53 nucleotide excision repair [97]. And regulator post-transcriptional activity included phosphorylation, acylation, proliisomer aisation, and sumoylation and post-translation changes.

9. p53 ROLE IN DIFFERENT CANCERS

The polymorphism at codon 72 variant is an intragenic modifier of mutant p53 [98]. Other studies in colorectal [99], lung [100], and head and neck cancers [99] have also revealed that in Arg/Pro germline heterozygotes, the Pro allele is specifically lost and the Arg allele turns to mutated. The codon 72 Pro/Pro genotype was correlated with an increased risk of lung cancer [101]. Another study showed that the Arg/Pro genotype plays a role in the heritable incidence of smoke-related lung carcinoma [102], but inconsistent results were reported in six other case-control studies [103]. A huge study revealed that there is no association with frequent P53 polymorphisms in breast cancer [104] and ovarian cancer [105]. A study reveals an eightfold elevated risk with the intron 3 variant in ovarian cancer patients [106] and 1.93 fold risk association showed with intron 6 polymorphism in the rare Msp1 allele carried ovarian cancer patient [107]. One more study explains intron 3 polymorphism as a causative factor in sporadic and familial breast cancer [108**],** these results also show inconsistent association with other studies [109-111]. Although a statistically significant association in p 53 intron 6 polymorphisms showed major risk in breast and colon cancers [112]. Rare C allele polymorphism detected in sporadic breast cancer patients in Americans with high-level mutant protein p 53 [113]. But there was no association observed in Polish cancer patients with p53 germline mutations [114]. The mutations of p53 gene of all cancers are regulated by C to T transitions with the mutational methylated CpG sequences. The increased risk of G to T transversions was expressed in lung cancers of smokers than the nonsmokers and with other cancers [115]. Subcellular disruptions of wild-type p53 was highly expressed in the cytoplasm of the undifferentiated neuroblastoma [116]. Irregular cytoplasmic p53 locations are mainly seen in human primary breast cancers, colon cancers and hepatoblastomas [117].

10. CONCLUSION

This review represents that the chronic inflammation involved in tumor development and progression, TNF acts as a major pro-inflammatory cytokine and also acts as an endogenous tumor promoter to regulate inflammation and carcinogenesis in different cancers. Tumor necrosis factor constitutes a representative index of inflammation activity and hence implicates cell damage in the evolving defects in a resolution of inflammation in carcinogenesis. Even though several cell culture and animal studies are available but natural chronic inflammatory agents and their true potential will be identified from the study of the genes with their functional mechanisms in cancer development is needed for future experimental, clinical trials. The inactivation of XRCC1 DNA repair genes leads to an important aspect in cancer initiation and progression by lack of genomic stability, with multiple effects leading to malignancies. The p53 gene regulates the tumor suppressions with a nuclear transcriptive action including a pro-apoptotic function in oncogenic potential. DNA damage by cellular stresses exhibits in pro-apoptotic function. Activated p53 influences cell cycle arrest to allow DNA repair and/or apoptosis to prevent the major DNA damage through the transactivation of its target genes. Thus, the DNA-binding activity of p53 is strongly linked to its tumor suppressive action. The regulatory mechanisms of p53 and also p53-mediated therapeutic strategies is helpful to cure different cancers.

Individual differences in mechanism of these genes are to be more crucial for the development of malignancies. However, the study of these particular genes and their functions is a greater pathway for future clinical aspects and molecular

therapies to improve the survival rate of the victims.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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