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REVIEW ARTICLE

IMPLICATIONS AND POTENTIAL ROLE OF HUMAN TELOMERASE REVERSE TRANSCRIPTASE (*hTERT*) IN BLADDER CARCINOGENESIS

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Abstract

Bladder cancer is a heterogeneous disease and ranks as 10th most common cancer worldwide. Urothelial carcinoma (UC) is the most common histologic type of BC and majority constitute of papillary tumors that are well-differentiated (low-grade). Several genetic changes may occur in bladder cancer, but hTERT promoter mutations and its expression has been detected in most cases of transitional cell carcinoma. Numerous researches have led to the findings which suggest that the hTERT promoter mutations in conjunction with the common polymorphism and hTERT expression have potential of being used as clinical biomarkers in bladder cancer. Further studies need to explore the potential use of hTERT gene in bladder cancer detection, diagnosis and prognosis. This review focuses on the role of hTERT in bladder tumors in the backdrop of various studies published.

Introduction:-

Bladder cancer (BC) is the most common malignancy of the urinary system. Every year, around 10 million individuals are reported to die from cancer. Urinary bladder cancer (UBC) accounts for about 3.0% of all new cancer diagnoses and 2.1% of all cancer deaths[1].Bladder cancer is the 10th most prevalent cancer in the world, with an estimated 549,000 new cases and 200,000 deaths per year. Bladder cancer is more prevalent in men than in women, with incidence and death rates of 9.6 and 3.2 per 100,000 in men, respectively, about four times those of women worldwide. As a result, the disease is more frequent in males, who have bladder cancer as the sixth most common cancer and ninth main cause of cancer death[1]. According to an epidemiologic survey conducted by Arshad et al. in a leading Kashmiri hospital, bladder cancer was recorded as the seventh most common cancer in Kashmir, with an incidence of 5.9%[2]. BC is associated with a number of recognized risk factors. Cigarette smoking is the major risk factor for bladder cancer, aside from certain occupational exposures to chemicals and water pollutants. Smokers have a 2 to 6 times higher risk of BC than non-smokers; the risk varies depending on the intensity and duration of smoking.With the growing frequency of smoking among women, the attributable risk has surpassed that of males in the United States, with 50% of bladder cancer cases in both sexes due to smoking[3].The most common histologic type of BC is urothelial carcinoma (UC) (approximately 90%). Bladder cancers are categorized based on differentiation as low grade (grades I and II) or high grade (grades III and IV) by the World Health Organization

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(2016). The distinction between low-grade and high-grade urothelial carcinoma has consequences for risk stratification and patient management. At the time of diagnosis, 70% to 80% of UCs are superficial, exophytic, papillary tumors that are well-differentiated (low-grade) and do not penetrate the epithelial basement membrane. These tumors are named as stage pTa.Stage pT1 refers to tumors that have infiltrated the basement membrane but have not entered muscle, whereas stage pT2 refers to tumors that have invaded muscle. Invasive UCC (urothelial cell carcinoma) is thought to develop through a distinct pathogenetic pathway from low-grade noninvasive UCC[4]. The first pathway leads to papillary lesions, whereas the second leads to flat lesions.Hyperplasia and/or minimal dysplasia usually gives rise tolow-grade papillary tumors and are characterized by loss of heterozygosity (LOH) of chromosome 9 and activating mutations of fibroblast growth factor receptor 3 (FGFR3), telomerase reverse transcriptase (*hTERT*), phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA) and inactivating mutations of STAG2. As a result of CDKN2A loss, low-grade papillary non-muscle-invasive BC can develop to muscle-invasive BC. Flat dysplasia or carcinoma in situ (CIS) induce muscle-invasive BC; the lesions include TP53 mutations and LOH of chromosome 9 (Figure 1). The invasive carcinoma can then acquire RB1 and PTEN loss, including other changes, resulting in metastatic potential[5]. Several studies have suggested that the telomerase reverse transcriptase (hTERT) gene plays an important role in conferring risk to bladder cancer.

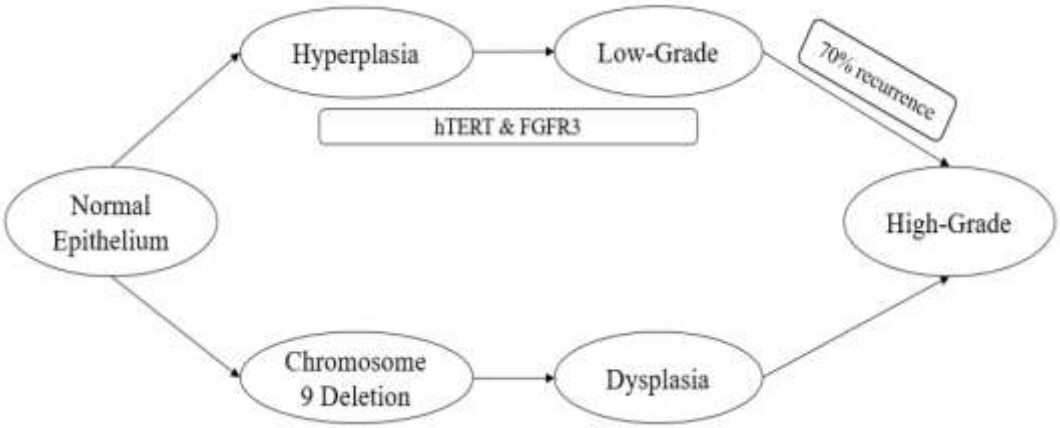

Figure 1:- Divergent molecular pathways of oncogenesis in urinary bladder cancer.

Telomerase reverse transcriptase (*hTERT***)**

Telomerase reverse transcriptase (abbreviated TERT, or hTERT in humans) is a catalytic subunit of the enzyme telomerase that, together with the telomerase RNA component (TERC), comprises the most important unit of the telomerase complex. It has 16 exons and 15 introns covering 35 kb and is found on the short (p) arm of chromosome 5 at location 15.33 (5p15.33)[6]. The hTERT gene's core promoter is made up of 330 base pairs upstream of the translation start site (AUG) and 37 base pairs of exon 2 of the hTERT gene[7]. The hTERT promoter is GC-rich and lacks TATA and CAAT boxes, but it includes several transcription factor binding sites. As a result, a high level of regulation by multiple factors in diverse cellular contexts is seen. The addition of nucleotides in a 'TTAGGG' sequence to the chromosomal ends (telomeres) is catalyzed by *hTERT*. The addition of repetitive DNA sequences prevents chromosomal ends from degrading after several rounds of DNA replication. Due to the significant involvement of hTERT/telomerase in oncogenesis, its regulatory mechanism has been a major subject in cancer research. hTERT expression is controlled at numerous levelsby several factors, but it is primarily regulated at the transcriptional level. In 90% of human malignancies, the telomerase enzyme is activated in somatic cells, resulting in unregulated cell proliferation and division, which eventually leads to tumor development. Nearly 90% of cancer cells have detectable telomerase activity, for instance, 75% of oral carcinomas, 80% of lung cancers, 84% of prostate cancers, 85% of liver cancers, 93% of breast cancers, 94% of neuroblastomas, 95% of colorectal cancers, and 98% of bladder cancers[8]. Telomerase activity is *controlled* at several levels, including transcription, mRNA splicing, and maturation and modification of *hTERT* and hTERC. In the regulation of telomerase expression, hTERT appears to be the major determinant.

Telomere length and Bladder cancer

Telomeres are specialized structures, found at the ends of eukaryotic linear chromosomes, which restrict chromosomal end-to-end fusion and contribute to genomic stability. Telomeres in most somatic tissues shorten 50 to 150 base pairs after each cell division, limiting the replicative capacity of normal somatic cells, which do not express telomerase in general[9]. On the other hand, telomeres do not shorten with time in germ line tissues and

malignancies, using various mechanisms[10]. Telomere changes are seen during carcinogenesis in this fashion, and telomere shortening appears to be one of the earliest and most common genetic changes in varioushuman malignancies[11,12]. The vast majority of human malignancies maintain their telomeres after tumor initiation by activating the enzyme telomerase or, in a minority of instances, via an alternative pathway known as alternate telomere lengthening[13]. Telomere length in solid tumors has been reported in a number of studies to have the potential to be utilized as a prognostic indicator. The research area has been reviewed before[14], and several studies have looked at the role of telomere length. The relationship between tumor telomere length and clinical prognosis has been studied in a variety of tumor types. The majority of research have discovered links between altered tumor telomere length, such as attrition and/or elongation, and poor prognosis. Reduced telomere content has been linked to worse survival in both breast and prostate carcinomas by Griffith group[15, 16].Short telomere length has also been associated to genomic instability and poor survival in sarcoma[17]. In hepatocellular carcinoma[18], colorectal cancer[19], Barrett carcinoma[20], and head and neck malignancies[21], long telomeres or a high tumor to non-tumor telomere length ratio, have been linked to tumors in advanced stages and a poorer prognosis. Telomere length abnormalities have previously been found to arise early in the carcinogenic process[13, 22]. The link between longer telomeres and a worse clinical outcome can only be speculated upon.As for different tumour types, it's plausible that telomerase is more strongly expressed in advanced tumor. Meeker et al. found that 29% of cancer precursor lesions, notably bladder lesions, had substantial telomere heterogeneity utilizing a recently developed FISH method for direct telomere length assessment in formalin-fixed human tissue specimens. In bladder specimens, these researchers discovered abnormally short or abnormally long telomeres[22]. In a study led by Jesus Fernandez-Gomez, telomere length in bladder washing samples was shown to be longer in tumors that were more aggressive. Patients with aneuploidy tumors had considerably longer telomeres than those with diploid cancers. In diploid cancers, they also discovered longer telomere length as the stage and grade advanced[23].

hTERT gene polymorphism and Bladder cancer

Several studies have found a statistically significant link between hTERT gene variants and cancer risk, including bladder cancer[24-29]. These findings clearly showed that hTERT genetic polymorphism confers a risk of cancer pathogenesis. hTERT rs2736100 and rs27360989 are single nucleotide polymorphisms (SNPs) found in intron 2 and exon 2 of the hTERT gene, respectively, and have been related to the risk of cancer development by several studies. However, the findings are still contradictory and inconsistent. Many well-designed genome-wide association studies (GWAS) have linked polymorphisms at the 5p15.33 locus (which contains the hTERT gene) to cancer risk at different sites. Lung cancer, basal cell carcinoma, and pancreatic cancer all exhibited a substantial relationship in these studies, whereas bladder cancer, prostate cancer, cervical cancer, and glioma revealed risk alleles in this region[30]. The biology of hTERT suggests that it might be a promising candidate gene for a variety of factors linked to cancer risk[31], and the hTERT gene has been identified as one of the most prevalent tumour markers. The rs2736100 single nucleotide polymorphism (SNP) is one of the most frequently reported hTERT gene variant that has been linked to cancer risk in several studies[24-27].Manuela Gago-Dominguez et al. found that hTERT rs2736100 has a major impact in bladder cancer[32]. Numerous studies have shown that hTERTrs2736098 polymorphism possess diverse effects in different cancer types[28, 29, 33, 34] (Table 1). In multiple investigations, hTERT rs2736098 has been identified as a risk factor for bladder cancer[32, 35-38]because it affects telomerase activity, increasing cancer incidence and development[30].Several studies, however, found that the hTERT rs2736098 polymorphism is not linked to the incidence of BC[39, 40]. The biology of *hTERT* suggests that it might be a promising candidate gene for a variety of factors linked to cancer risk[31], and the hTERT gene has been identified as one of the most prevalent tumor markers.

Numerous cancer types have shown the presence of telomerase activity. Nonetheless, their existence does not always indicate malignancy. In various studies, increased hTERT expression has been linked to cancer pathological grade and clinical stage. The function of hTERT in bladder cancer detection and diagnosis has received a lot of attention. Most of the findings suggest that hTERT gene might be useful in detecting the cancer. In most instances of transitional cell carcinoma, hTERT promoter mutations and hTERT expression have been found. hTERT promoter mutations have been discovered at high frequency in a wide range of malignancies, but not in surrounding normal tissue[41,42]. THOR (TERT hypermethylated oncological region) hypermethylation has also shown to play a role in the activation of hTERT expression and multiple clinical research have looked at hTERT promoter DNA hypermethylation in human carcinoma[43,44] as a possible biomarker of *hTERT* expression, cancer development, and/or patient survival during the last decade. Demethylation of THOR, which is unique to cancer cells, may prove to be a new therapeutic approach for inhibiting hTERT expression without harming healthy tissue.

Table 1:- Summary of the research's assessing hTERT gene polymorphism.

hTERT polymorphism	Author	Year	Cancer type	Association	References
rs2736100	ByungJoon Choi	2015	Gastric cancer	Yes	ByungJoon Choi et al 2015
	Qing Sun	2020	GN/CKD	No	Qing Sun et al 2020
	Mocellin	2012	Testicular cancer	No	Mocellin et al.,2012
	Kinnersley	2012	Colorectal cancer	Yes	Kinnersley et al.,2012
	Manuela Gago-Dominguez	2010	Bladder cancer	Yes	Manuela Gago-Dominguez et al 2010
	Yan-li Xing	2016	NSCLC	Yes	Yan-li Xing, et al 2016
	Tingyuan Pang	2017	Lung, bladder, breast,CRC	Yes	Tingyuan Pang et al 2017
rs2736098	Tingyuan Pang	2017	HCC and SCCHN	No	Tingyuan Pang et al 2017
	Ru Wang	2019	Bladder cancer	Yes	Ru Wang et al 2019
	Jaworowska	2011	Bladder cancer	No	Jaworowska et al. 2011
	Ma	2013	Bladder cancer	No	Ma et al. 2013
	Jin Eun Choi	2009	Lung cancer	Yes	Jin Eun Choi, et al 2009
	Savage SA	2007	Breast cancer	Yes	Savage SA, et al., 2007
	Rafnar T	2009	lung cancer, bladder cancer, prostate cancer	Yes	Rafnar T, et al., 2009
	Yan-li Xing	2016	NSCLC	Yes	Yan-li Xing, et al 2016
	Manuela Gago-Dominguez	2010	Bladder cancer	Yes	Manuela Gago-Dominguez et al 2010
	Mohammad Hashemi	2014	Breast cancer	Yes	Mohammad Hashemi et al 2014

Conclusion:-

hTERT, a vital defense of genomic integrity is accountable for maintenance of telomere. All the hTERT signature like mutations, sequence variations and expression play an important role in hallmark of carcinogenesis that primarily includes bladder cancer.

The predictive influence of hTERT promoter mutations and polymorphic sequence variants makes it potential clinical biomarker. Still challenging disputes remain for hTERT promoter methylation and its relation with its expression while telomere length has demonstrated as an effective prognostic factor. There are number of significant queries and trials that remain to be answered like the vast changing scenario of mutations in different tumors, connection among the mutant promoter and numerous extra hTERT signalling regulation effects for its potential to inhibit telomerase in dysplastic cells?

Conflict of interest:-

Authors declare no conflict of interest.

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