



International Journal of
Cancer Research

ISSN 1811-9727



Academic
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Introduction to the Role of Fragile Histidine Triad (*fhit*) Gene in Cancer: A Review of Literature with Special Emphasis on Cervical Carcinoma

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ABSTRACT

The role of fragile histidine triad (*fhit*) gene in the etiology of cancer is a relatively recent area of research. The *fhit* gene has been investigated in most cancers; however, literature is not conclusive regarding its role in the pathophysiology of cancer. Many studies are now focusing on this gene and its potential relationship with cancers. Although, studies have shown an association between infection with Human Papillomavirus (HPV) and cervical neoplasia, evidence also suggests that this infection alone is not sufficient for development of cervical cancer. Other genetic factors like altered tumor suppressor gene activities are also thought to contribute to the carcinogenic process in cervical carcinomas. In this short review, we present the function, the potential role of *fhit* gene and its protein, influence of *fhit* gene in various cancers with specific emphasis on cervical cancer has been discussed. In addition, the present article also focuses on the biochemical and molecular nature of FHIT protein.

Key words: Fragile histidine triad gene, *fhit*, cancer, cervical cancer

INTRODUCTION

Exposure to carcinogens and the associated FHIT inactivation was first observed in lung cancers (Sozzi *et al.*, 1998), suggesting that the alteration of the *fhit* gene through damage to the associated fragile region by carcinogens may contribute in a large part to the pathophysiology of cancer. The loss of FHIT function was more frequently observed in cancers developing in individuals with constitutional alterations to genes involved in DNA repair (Mori *et al.*, 2001). Epigenetic changes to chromatin, such as DNA methylation and modifications in histone proteins regulate transcription of several tumor suppressor genes (Hsieh and Jones, 2003). Multiple genetic changes, including activation of protooncogenes to oncogenes and epigenetic modification (inactivation) of tumor-suppressor genes are involved in the pathogenesis of cancer (Hsieh and Jones, 2003; Pichiorri *et al.*, 2008). Such genetic changes affect cell survival, cell proliferation and stability of the genome. The 3p14.2 region in chromosome 3 which harbors the *fhit* gene encompasses the most active common fragile sites of the human genome making the region very sensitive to alterations by DNA damaging agents (Pichiorri *et al.*, 2008).

Aberrant transcripts of the *fhit* (fragile histidine triad) gene have been reported in human cancers (Ohta *et al.*, 1996; Sozzi *et al.*, 1996; Mao *et al.*, 1996), supporting evidence also indicates the role of FHIT protein in the regulation of apoptosis and cell cycle (Sard *et al.*, 1999). Knockout mice models become highly susceptible to chemical induction of tumors and cells without FHIT protein showed increased resistance to ultra-violet radiation, mitomycin C and ionizing radiation (Ishii *et al.*, 2007). Ishii *et al.* (2006) suggested that FHIT protects cells from accumulating DNA damages, through modulation of checkpoint proteins Hus1 and phosphoChk1.

Protein biochemistry: FHIT belongs to the histidine triad superfamily (HIT, characterized by the histidine triad motif, HxHxHxx (where, x is a hydrophobic residue)) of nucleotide-binding proteins and is functionally a diadenosine triphosphate hydrolase which under *in vitro* conditions cleaves diadenosine triphosphate through a magnesium dependent hydrolysis to adenine diphosphate and adenine monophosphate (Barnes *et al.*, 1996). In humans, this enzyme is composed of 147 amino acids (Ohta *et al.*, 1996; Pekarsky *et al.*, 1998) and is involved in purine metabolism. In the first step of enzymatic hydrolysis, it is hypothesized that diadenosine triphosphate and Mg(2+) reacts with the His96 residue of the enzyme to form a covalent FHIT-AMP intermediate releasing Mg-ADP; this intermediate in the second step releases AMP (Barnes *et al.*, 1996; Abend *et al.*, 1999). Barnes *et al.* (1996) showed that the FHIT substrates, diadenosine triphosphate and diadenosine tetraphosphate are involved in intracellular functions such as regulation of DNA replication and signaling stress responses. Direct evidence of this mechanism was provided by Huang *et al.* (2004), who showed that FHIT protein mutated at His96 region is completely inactive against Mg-diadenosine diphosphate indicating that conserved residues of the histidine triad are required for activity of the enzyme.

The FHIT protein is homologous to the Aph1 enzyme of *Saccharomyces pombe*, which has diadenosine triphosphate hydrolase activity, a function that is conserved from yeast to human. Structural studies have shown that binding of the FHIT dimer with two molecules of diadenosine triphosphate, results in highly phosphorylated surfaces, with potential signaling activity (Pace *et al.*, 1998; Pekarsky *et al.*, 2004). The FHIT protein may exist in unphosphorylated, monophosphorylated and diphosphorylated forms.

The 16.8 KDa protein produced by the expression of the *fhit* gene is phosphorylated at tyrosine 114 residue by Src family proteins. The structure of the FHIT protein along with active sites predicted by Thematics is shown in Fig. 1. The FHIT protein is expressed at the highest steady state

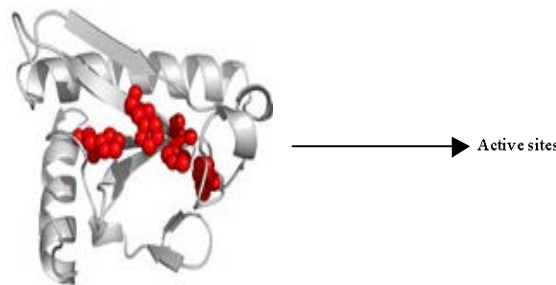


Fig. 1: FHIT protein with active sites. Active sites of the FHIT protein as predicted by Thematics. Human fragile histidine triad protein (E.C. 3.6.1.29; PDB: 5FIT). Adapted from: Wei *et al.* (2007)

levels in the kidney and liver. The protein is primarily cytosolic, but is also found in the mitochondria. Restoration of *fhit* gene expression in cancer cells deficient in this gene causes death by apoptosis, involving the intrinsic caspase pathway, in cancer-derived cells and in tumor xenografts. The tumor-specific loss or reduction of FHIT protein has been detected immunohistochemically in cervical carcinoma (Greenspan *et al.*, 1997).

Interactions of FHIT with other proteins: The biological function of FHIT protein was characterized using the yeast two-hybrid screen by Shi *et al.* (2000). FHIT was shown to interact with the protein UBE2I, this sequence was found to be identical to that of human ubiquitin-conjugating enzyme 9 (hUBC9). A single amino acid substitution at codon 96 from histidine to asparagine (His_Asn) or three amino acid substitutions (His_Asn) at codons 94, 96 and 98 did not affect this association. The enzymatic activity of FHIT was eliminated by mutations in either of the histidine triad regions indicating the potential role for this protein in controlling cell cycle.

Studies of Weiske *et al.* (2007) showed that FHIT protein is associated with a lymphoid enhancer-binding factor-1, T-cell factor and beta-catenin complex in human embryonic kidney cells. FHIT was shown to be bound to the C-terminal domain of beta-catenin, a protein which plays a vital role in the Wnt signalling pathway.

Mutations in *fhit* gene: The *fhit* (fragile histidine triad) gene spanning more than 1.6 Mb of the genomic DNA is a tumor-suppressor gene composed of 10 exons. The gene encodes a 1.1 kb mRNA. The most common fragile site, FRA3B is located within the *fhit* gene (Ohta *et al.*, 1996). It has been shown that the degree of chromosomal fragility at this particular site may determine the degree of susceptibility to cancer (Yang *et al.*, 2002). The *fhit* region also encompasses the break point of the t(3:8) translocation (Fig. 2), identified in familial renal-cell carcinoma. Using transfection experiments in 4 different cell line with homozygous deletions of the *fhit* gene, Croce *et al.* (1999) demonstrated the tumor suppressor activity of this gene. The FHIT-expressing transfectants when injected into nude mice resulted in the loss of the ability to form tumors (Siprashvili *et al.*, 1997). Ohta *et al.* (1996) showed that three 5-prime exons of FHIT are centromeric to the 3p14.2 breakpoint, while the remaining exons are telomeric to this region (Fig. 3). Using FHIT gene knock-out mouse embryonal stem cells, Fong *et al.* (2000) and Zanesi *et al.* (2001) have shown that the *fhit* ^{-/-} knockout mice depicted increased susceptibility to spontaneous tumors and high sensitivity to carcinogens. Aberrant *fhit* gene transcripts have been found in esophageal, stomach and other carcinomas. A pseudogene, with sequences nearly identical to the 5'UTR of FHIT, was found to be located on chromosome 1 (www.atlasgeneticsoncology.org/Genes/FHITID192ch3p).

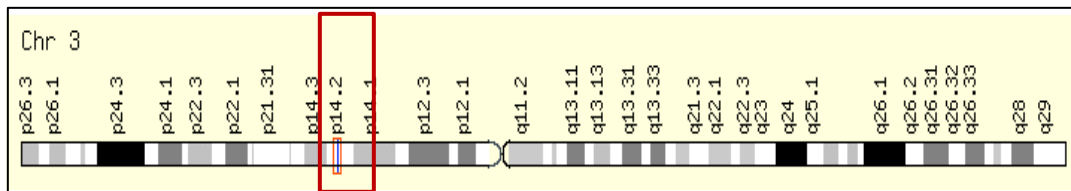


Fig. 2: Chromosomal location of *fhit* gene. The 3p14.2 region in chromosome 3 which harbors the *fhit* gene. Adapted from: <http://www.genecards.org/cgi-bin/carddisp.pl?gene=Fhit>

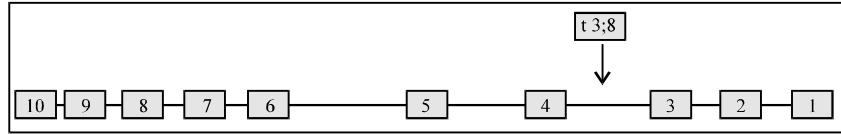


Fig. 3: Exons of *fhit* gene. Three 5-prime exons of FHIT are centromeric to the 3p14.2 breakpoint, while the remaining exons are telomeric to this region. The figure shows the *fhit* gene genomic locus with exons and the position of t(3;8) translocation. Redrawn based on image from: www.cancerindex.org/clinks3h.htm

Corbin *et al.* (2002) suggested the probable presence of multiple hot spots within the FHIT/FRA3B locus. Their experiments involved microcell-mediated chromosome transfer to isolate hybrid cell clones that retain chromosome 3 homologues followed by molecular mapping of the FHIT/FRA3B locus. Their results also suggest that factors other than the DNA sequence alone may be responsible for DNA breaks/gaps.

Implications of *fhit* gene mutations: Some of the *fhit* gene polymorphisms that have been most commonly observed in human cancers include the below:

524	A/G (exon 6)	Silent mutation
545	G/A (exon 6)	Silent mutation
626	C/T (exon 7)	Silent mutation
651	G/T (exon 8)	Valine to phenylalanine
656	T/C (exon 8)	Silent mutation
Several intronic splice regions		

Adapted from: www.atlasgeneticsoncology.org/Genes/FHITID192ch3p

Homozygous deletions in *fhit* gene in lung, gastrointestinal, breast and head-and-neck cancers and aberrant *fhit* transcripts in cancer cell lines have been reported (Ohta *et al.*, 1996; Sozzi *et al.*, 1996; Negrini *et al.*, 1996; Virgilio *et al.*, 1996; Druck *et al.*, 1997). However, aberrant *fhit* transcripts have been seen in histologically normal tissues (Latil *et al.*, 1998). Although, Fong *et al.* (1997) have reported that the point mutation of the *fhit* gene is rare in lung cancer, Yoshino *et al.* (1998) in contrast found 9 point mutations (19%) in cervical carcinomas and showed that these are somatic mutations rather than rare polymorphisms or germline mutations.

Animal models to investigate the role of *fhit* gene: After inactivation of the *fhit* allele, the resultant mice carrying the inactivated *fhit* allele (+/-) were treated with nitrosomethylbenzylamine. While only 25% of the +/+ mice developed adenoma or papilloma, 100% of *fhit* deficient mice developed multiple tumors. The visceral and sebaceous tumors, which lacked FHIT protein, were similar to the tumors found in the Muir-Torre familial cancer syndrome (Fong *et al.*, 2000).

Zanesi *et al.* (2001) suggest that the *fhit* gene may be a one-hit tumor suppressor gene in some tissues. Dumon *et al.* (2001) inhibited tumor development by *fhit* gene transfer using viral vectors suggesting that *fhit* gene therapy could be a novel clinical approach in cancer. Shiraiishi *et al.* (2001) sequenced >600 kb of the mouse locus and determined the *fhit* deletion breakpoints in a

mouse kidney cancer cell line. Sequence alignment of the murine and human FRA3B sequences showed that this region was stable in evolution. There were also several unusual highly conserved regions.

Role of FHIT in various cancers: The inactivation of *fhit* gene was shown in a variety of human malignancies indicating its the tumor suppressor function. In approximately 50% of gastrointestinal carcinomas (esophageal, stomach and colon) aberrant *fhit* transcripts have been identified (Ohta *et al.*, 1996). Huebner and Croce (2003) showed that FHIT is altered in many human tumors caused by environmental carcinogens. The same authors in a previous study (Huebner and Croce, 2001) showed that *fhit*-negative cancer cells were highly sensitive to the *fhit* expression. Geurts *et al.* (1997) reported that FHIT was involved in a translocation-derived fusion with the high-mobility group (non histone chromosomal) protein isoform I-C, the causative gene in a variety of benign tumors. Using sequencing and Southern blot analysis, Rassool *et al.* (1996) found neither (CGG)_n repeats nor other sequences associated with rare fragile sites within the 85 kb contig.

By sequence analysis of *fhit* locus and 22 associated cancer cell deletion endpoints, Inoue *et al.* (1997) demonstrated that this locus is a frequent target of homologous recombination resulting in *fhit* gene internal deletions. Corbin *et al.* (2002) suggested the possibility of existence of the presence of multiple hot spots within the *fhit* locus using microcell-mediated chromosome transfer.

Lung cancers: The expression of the FHIT protein and its relevance to the diagnosis and prognosis of lung cancers were studied by Feng *et al.* (2007) wherein a total loss or marked reduction of expression was seen in 67% of the analyzed cases. This loss or marked reduction of *fhit* gene expression was lung cancers of smokers. However, the expression of FHIT was not associated with histopathologic grading of tumors and their clinical staging, lymph node metastasis or survival time. The correlation between loss of *fhit* gene expression with a large number of molecular genetic and clinical parameters in Non-Small-Cell Lung Cancers (NSCLC) were studied using a polyclonal antibody to FHIT protein. A complete loss of cytoplasmic FHIT staining was seen in this immunohistochemical reaction in more than 50% of tumors.

Using reverse transcriptase polymerase chain reaction, Sozzi *et al.* (1996) analyzed the structure of *fhit* gene in small cell and non-small cell lung cancers. The authors noted abnormal-sized transcripts in tumors and loss of heterozygosity for microsatellite markers in and regions adjacent to *fhit* locus. In these tumors, inactivation of the *fhit* gene occurred loss of 1 allele and altered expression of the remaining allele.

Studies have indicated a role of cigarette smoking in the etiology of lung cancer. Microsatellite alterations within the *fhit* gene and at an independent locus in chromosome 10 called D10S197 were assessed in lung tumors from heavy smokers and in tumors from never smokers (Sozzi *et al.*, 1997a). Loss of heterozygosity affecting at least one locus of the *fhit* gene was observed in 80% tumors from the smokers group and only in 22% tumors from non-smokers. While, the loss of *fhit* in smokers and nonsmokers was statistically significant, no difference in loss of heterozygosity rate was observed at D10S197 locus. An analysis of lung cancer cell lines, small cell lung carcinomas and pairs of non-small cell primary tumors and bronchial mucosa specimen using molecular, genetic and histochemical methods showed concordance between RNA abnormalities and lack of FHIT protein expression in lung tumors and cell lines (Sozzi *et al.*, 1997b). This study also suggested that FHIT protein may be lost at very early stages of lung carcinogenesis. In addition, Stein *et al.* (2002)

showed that active smokers had a significantly higher frequency of fragile site expression, compared to nonsmokers and SCLC patients who stopped smoking. Active tobacco exposure may thus increase the expression of *fhit* gene.

Head and neck cancers: Virgilio *et al.* (1996) noted several regions of loss of heterozygosity in head and neck cancers. More than 90% of the analysed head and neck squamous cell carcinoma cell lines showed alterations of at least 1 allele of the *fhit* gene. Using immunohistochemical analysis Paradiso *et al.* (2004) hypothesise that decreasing levels of FHIT is directly involved in cancer development.

Thyroid tumors: A retrospective analysis of *fhit* mRNA transcripts and genomic DNA from thyroid tumors showed the frequent present of truncated *fhit* transcripts alongwith full-length transcripts (McIver *et al.*, 2000). The pathogenetic role for these aberrant transcripts remains a possibility, but no correlation was found with stage, histological grade or outcome in this study.

Colorectal cancers: Morikawa *et al.* (2000) reported altered expression of FHIT protein in 47% of colorectal adenomas. The amount of FHIT protein produced was inversely proportional to the degree of dysplasia. Their findings suggest that altered expression of the *fhit* gene is an early event in the etiology of colorectal cancer. Elnatan *et al.* (1999) showed that the HIT family of genes were selectively involved in tumorigenesis and also confirmed the early alterations in *fhit* gene expression. The alteration of the *fhit* locus and loss of FHIT protein expression were found to be significantly more frequent in sporadic colorectal carcinomas (Mori *et al.*, 2001).

Bladder cancer: Maruyama *et al.* (2001) investigated the aberrant promoter methylation profile of bladder cancers and correlated their data with clinicopathological findings. The methylation profile was hypothesised to be a potential new biomarker of risk prediction in bladder cancer.

Esophageal cancer: In esophageal cancer, 50% of severe and moderate dysplasias and 33% of mild dysplasias were *fhit* negative in most of the *in situ* lesions (Mori *et al.*, 2001). Mimori *et al.* (2003) showed that microsatellite instability is significantly related to the allelic loss in the *fhit* region and this was unrelated to the progression of esophageal cancer.

Hepatocellular cancer: Zekri *et al.* (2005) showed that the *fhit* gene is a frequent target in hepatitis C virus-associated hepatocellular carcinoma and that alterations affecting this gene occurs as an early event in this type of neoplasm. In addition, studies also showed abnormal apoptosis-proliferation balance indicating an important role of *fhit* gene expression in the carcinogenesis and development of hepatocellular carcinoma (Nan *et al.*, 2005).

Prostate cancer: A linkage analysis by of 80 candidate genes conducted in prostatic adenocarcinoma showed that involvement of germline variations of FHIT may increase the risk of prostate cancer risk (Larson *et al.*, 2005).

Breast cancer: The protective role of *fhit* gene was determined by crossing in mice carrying one inactivated *fhit* allele with mice carrying the rat neu proto-oncogene (Bianchi *et al.*, 2007). All *fhit* heterozygous mice developed mammary tumors, whereas when both *fhit* alleles were present,

tumor incidence was reduced in 27% of the mice. Their findings suggest a protective role for FHIT in HER2-driven mammary tumors.

The loss of heterozygosity in D3S1300, an *fhit* intragenic marker with concomitant loss of BRCA1 intragenic marker was reported (Santos *et al.*, 2004). In this study, no correlations were found between loss of heterozygosity with the size of tumor, grade and axillary lymph node metastasis. Guler *et al.* (2004) observed a strong correlation between FHIT and Wwox expression, a result consistent with the increased susceptibility of fragile sites to DNA damage. The reduced expression of *fhit* expression was associated with adverse prognostic factors. In an additional study Guler *et al.* (2009) showed that reduced expression levels of FHIT, Wwox and nuclear AP2gamma have roles in basal-like differentiation in breast cancer. In addition, Wang *et al.* (2008) have shown that the expression of *fhit* gene and Wwox and decreases along with progression from normal cells to cancer.

Gastric cancer: The absence of FHIT protein correlated with tumor stage and histologic grade in gastric cancers (Capuzzi *et al.*, 2000). Lee *et al.* (2001a, b) showed that a higher frequency of aberrant transcripts in gastric carcinomas. Along with this, they observed a significant rate of loss of heterozygosity indicating the important role of *fhit* gene in etiology of gastric carcinogenesis. A study by Zheng *et al.* (2007) showed that in gastric cancer, the expression of *fhit* and *pten* were lower compared to the levels in normal mucosal cells. A negative association was found with the extent of lymphatic invasion, lymph node metastasis, liver metastasis and staging. However, a positive association was found between *fhit* and *pten* gene expression.

Periocular sebaceous gland carcinoma: Holbach *et al.* (2002) showed that the inactivation of the *fhit* gene or inactivation of the mismatch-repair system may contribute to the development of periocular sebaceous gland carcinoma in Muir-Torre syndrome.

Renal carcinoma: Gemmill *et al.* (1998) showed that the reciprocal t (3;8) translocation was associated with multifocal clear cell renal carcinoma. Such balanced and constitutional translocation was also reported in bilateral clear cell renal cell carcinoma (Poland *et al.*, 2007), these translocations disrupt the *trc8* and *fhit* genes caused increased susceptibility to bilateral renal cell carcinoma. Strefford *et al.* (2005) reported genomic imbalances and rearrangements in renal cell carcinoma cell lines. The frequent loss or decrease in FHIT protein expression was also observed by Gayrard *et al.* (2008) in addition *fhit* inactivation was found to play a major role in renal cell tumorigenesis by Velickovic *et al.* (2001) and Sukosd *et al.* (2003).

Role of FHIT gene in cervical cancers: Loss of FHIT expression, was found to be reported commonly in patients with stage IA1 to IB2 cervical squamous cell carcinoma, this being significantly more common in cervical cancers of smokers (Holschneider *et al.*, 2005). Abnormal protein expression *fhit* gene has been reported to play a pivotal role in cervical cancers (www.cancerindex.org/clinks3h.htm), a common type of malignancy accounting for about 6% of all cancers found in women (Parkin *et al.*, 1999). Cervical cancer remains a major source of cancer-related morbidity and death for women throughout the world (Bosch *et al.*, 1995). The Human Papilloma Viruses (HPV) are the principal cause of cervical cancer and HPV DNA has been found in more than 95% of carcinoma cases. HPV are DNA viruses and affect the nucleus and the cytoplasm of the infected cells. The DNA of these viruses may or may not be intergrated in the

epithelial cell nuclei. However, morphological changes occur when HPV DNA is integrated into the epithelial cell nuclear DNA. The HPV lesions are typically dysplastic and atypical and may be associated with chromosome and ploidy alterations (Geradts *et al.*, 2000). Infection with certain high risk Human Papilloma Virus (HPV) types is associated with cervical cancer probably by inactivation of p53 and pRB through interactions with the HPV E6 and E7 proteins, respectively (Alani and Munger, 1998). HPV infections are generally transient, but a small percentage of women develop cervical cancer (Zur Hausen, 1990; Evander *et al.*, 1995).

Nevertheless, HPV infection alone may not be sufficient for the development of cervical cancer since this does not explain the additional events that are necessary for some infections to become chronic and undergo malignant transformation (Neyaz *et al.*, 2010). Genomic rearrangements, aberrant mRNA transcripts and decreased or complete absence of FHIT protein have been reported in cervical carcinomas (Noronha *et al.*, 1999; Lopez-Beltran and Munoz, 1995). These aberrations may have a predictive role in the malignant transformation of lesions in the cervix.

Becker *et al.* (2002) showed fragility of *fhit* gene in cervical cancer. The *fhit* gene expression on a panel of cervical tumor-derived cell lines showed aberrant regulation. In squamous-cell carcinomas of the uterine cervix, 43% of tumors were found with aberrant transcripts and 32% tumors with point mutations (Yoshino *et al.*, 2000). Alterations in *fhit* were significantly associated with cervical carcinogenesis. Further, this study analysed the alteration of *fhit* gene in various grades of cervical intra-epithelial neoplasias and invasive cervical carcinomas compared to normal cervical epithelium. A strong association of altered FHIT protein expression with the disruption of normal *fhit* transcript was observed. There was no correlation between *fhit* inactivation and HPV infection. The *fhit*-gene inactivation was shown to be a late event in cervical carcinogenesis. In addition, homozygous deletions of *fhit* in cervical cancer and cervical carcinoma cell lines have been reported (Muller *et al.*, 1998). Aberrant *fhit* transcripts were seen only in cervical tumor tissue and not in normal cervical tissue (Greenspan *et al.*, 1997; Muller *et al.*, 1998; Nakagawa *et al.*, 1999; Segawa *et al.*, 1999; Yoshino *et al.*, 2000), however, some studies have reported the same levels of RNA expression pattern in both tumors and normal cervical tissue (Chu *et al.*, 1998; Su *et al.*, 1998; Yoshino *et al.*, 2000).

A reduced FHIT protein level compared to normal cervical epithelium has been reported (Greenspan *et al.*, 1997; Segawa *et al.*, 1999; Birrer *et al.*, 1999; Yoshino *et al.*, 2000). 61% of squamous carcinomas and 40% of adenocarcinomas of the cervix showed abnormal *fhit* expression (Birrer *et al.*, 1999). *fhit* expression was abnormal in both glandular and squamous cervical cancers. Abnormal *fhit* expression was also detected in some preneoplastic lesions of the ectocervix. Alterations in *fhit* expression may be an important marker of early progression in cervical cancer.

Connolly *et al.* (2000) suggest that loss of *fhit* expression could serve as a useful marker of high-grade preinvasive lesions that have an increased likelihood to progress to invasive carcinoma. Baykal *et al.* (2003) showed that *fhit* gene was lower in 53% of the cervical carcinomas. None of the clinicopathologic prognostic parameters investigated in this study showed a correlation with FHIT expression. FHIT was thus shown to play a carcinogenic role in tumoral progression but not in the tumoral development.

Bahnassy *et al.* (2006) reported that aberrations in the *fhit* gene frequent in HPV-associated cervical carcinoma can be used as predictors of tumor recurrences. In addition to this, a decreased or complete absence of FHIT protein expression was found in 65% cases. The difference between the expression level of the *fhit* gene and the FHIT protein was reported by Birrer *et al.* (1999) and Bahnassy *et al.* (2006). Genomic rearrangements, altered mRNA transcripts and absence or

reduction of the FHIT protein have all been reported in numerous epithelial tumors including cervical carcinomas (Lopez-Beltran and Munoz, 1995; Munoz *et al.*, 1995; Noronha *et al.*, 1999). These aberrations may play a predictive role in the identification of the malignant potential of high-grade squamous intraepithelial lesions of the uterine cervix (Schiffman *et al.*, 1993).

Kannan *et al.* (2000) identified 2 different mutations in oral cancer (caused by chewing tobacco) and cervical cancer (caused by HPV) infection. These mutations were at the second nucleotide 3' to the termination codon (TGA) in exon 9 and at the ninth nucleotide upstream to the beginning of exon 9. In addition to this, the authors also reported a single nucleotide *fhit* gene polymorphism due to T/A replacement at 17 nucleotides upstream to exon 9.

Neyaz *et al.* (2008) analysed cervical cancer tissue biopsies of various clinical stages and histological grading. Aberrant promoter methylation of the *fhit* gene was found in 28.3% of subjects and was significantly ($p < 0.01$) associated with the cervical cancer compared with controls. Neyaz *et al.* (2010) also attempted to study the role of point mutation in *fhit* gene in HPV mediated cervical cancer and identified a novel mutation at codon 98 from with replacement of the amino acid His by Arg in cervical cancer. The authors suggest that the His to Arg substitution in the substrate-binding domain may generate catalytically inactive protein with consequent loss of tumor suppressor activity. Promoter hypermethylation and loss of heterozygosity of the *fhit* was investigated in cervical cancer (Choi *et al.*, 2007). While, promoter hypermethylation was detected in 24% of tumors compared to noncancerous tissues, no correlation was observed between loss of heterozygosity and promoter hypermethylation for *fhit* gene.

CONCLUSIONS

From the reviewed studies it can be said that, in addition to HPV infection, mutations in *fhit* gene may be critical for the development and progression of cervical cancer. In addition, from the literature, it is also clear that *fhit* gene might play an important role in the etiology of several other cancers, although supporting literature is limited. Host factors like altered tumor suppressor gene and activation of protooncogenes to oncogenes that contribute to the carcinogenic process in cervical carcinomas and other cancers need to be further evaluated to understand the specific role of this protein. The present review article focused on the biochemical and molecular nature of FHIT protein the role of this gene as evident from literature in various cancers with special emphasis on cervical cancer. However, to better understand this protein, further studies in larger population sizes and sub-divided into groups based on stages of cancers in necessary.

The data presented here are from a non-homogeneous collection of information available about *fhit* gene. This is indeed a potential limitation of the study. However, the article tries to give a clear picture of the important role the *fhit* gene plays in the pathophysiology of cancers. The article therefore focused on the summary of the gene, its protein, expression and its role giving an overall understanding of this gene and its protein.

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