Applied Cancer Research 2005; 25(2):51-57

REVIEW ARTICLE

TP53 Gene and Li-Fraumeni Syndrome

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ABSTRACT

Cancer is a disease that strikes most families and its devastating effects bring suffering and instability to both patient and family. Clustering of cancers in certain families is even more devastating, leading medicine to study its origin and ways to prevent it. Many cancer syndromes have been identified due to the repeated occurrence of specific tumors over a certain age-range. The rare cancer predisposition Li-Fraumeni syndrome (OMIM #151623; LFS) is transmitted in an autosomal dominant pattern, which predisposes affected individuals to an increased risk of developing a variety of cancers at an early age, including childhood. The most characteristic forms of cancers in LFS include soft-tissue sarcoma, breast cancers, brain tumors, and adrenocortical carcinomas. LFS is a dominantly inherited syndrome, frequently associated with germline mutations in the *TP53* gene (OMIM #191170), which encodes protein p53. This protein regulates cell cycle, apoptosis, DNA repair, differentiation, senescence and development. Activation of p53 prevents DNA replication and cell proliferation when cells are subjected to stress that may disturb genetic or genomic integrity. Thus, *TP53* acts as a major tumor suppressor gene by exerting simultaneous control on many components of the molecular mechanisms of carcinogenesis. Loss of p53 function may favor cancer development and explains predisposition in germline *TP53* mutation carriers. This review will discuss the main characteristics of *TP53*, its regulation, the consequences of its inactivation in cancer, the germline *TP53* mutation related to Li-Fraumeni syndrome and strategies for surveillance.

Key words: Li-Fraumeni syndrome. Genes, TP53. Genes, p53.

INTRODUCTION

Almost every form of cancer in humans has been reported to aggregate in families. The occurrence of cancer clustering in certain families is devastating, leading medicine to study its origin and ways to prevent it. These familial clusters could be inheritable mutated cancer-susceptible gene, though other explanations include odds association and exposure to environmental carcinogens.[1] Cancer predisposition syndromes have been identified by the repeated occurrence of specific tumors over a certain age-range.

In recent years, advances on novel techniques of molecular genetics have located and mapped some cancer-predisposing genes, including the hereditary retinoblastoma (*Rb*) gene, *WT1* gene for Wilms' tumor, the *APC* gene of familial polyposis coli, *BRCA 1* and *2* for Familial Breast and Ovarian Cancer Syndrome and the *TP53* tumor suppressor gene in Li-Fraumeni syndrome.[2] Li-Fraumeni syndrome is an autosomal dominant disorder of multiple cancers that are difficult to treat and often lethal. This review discusses the main characteristics of *TP53*, its regulation, the consequences of its inactivation in cancer, the germline *TP53* mutation related to Li-Fraumeni syndrome and to the main perspectives in the cancer management.

LI-FRAUMENI SYNDROME

In 1969, Li and Fraumeni reviewed medical files and death certificates from children with a histopathological diagnosis of

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rhabdomiosarcoma and found a high early onset cancer incidence among their relatives.[3] They presented different tumor types occurring over a wide age range, including childhood cancer. The first definition of the syndrome derived from Li and Fraumeni's work in 1988.[4] The Li-Fraumeni syndrome (LFS; OMIM# 151623) was then proposed as a cancer predisposition syndrome and it was subsequently confirmed by a series of epidemiological studies that detected a similar tumor pattern among family members.[5,6]

It was characterized by the incidence of a sarcoma, diagnosed before the age of 45 years, associated with the presence of other early onset tumors in first and second degree family members, which included breast cancers, brain tumors, and adrenocortical carcinomas (ADR) (Table 1). Other cancers, such as leukemia, lung cancer, skin melanoma, gastric, pancreatic, and prostate cancer were also described to be overexpressed in some families. In some cases, germcell tumors, choroid plexus papilloma, and Wilms' tumor have been reported as part of the spectrum. However, population-based data on tumor incidence in Li-Fraumeni families are still scarce and the exact spectrum of cancer diseases is still a matter of debate. A number of families present a tumor pattern that is reminiscent of LFS without matching the classical criteria and are termed Li-Fraumeni like (LFL)[7] (Table 2). Several definitions of LFL have been proposed (LFL-E1 and LFL-E2) (Table 3).[8,9]

Table 1 - Clinical criteria for Li-Fraumeni syndrome

Proband with a sarcoma diagnosed before 45 years of age
AND
First degree relative with any cancer under 45 years of age
AND
First- or second-degree relative with any cancer under 45 years or sarcoma at any age

Table 2 - Clinical criteria for Li-Fraumeni Like syndrome (Birch)

Proband with any childhood cancer or sarcoma, brain tumor, or adrenocortical tumor diagnosed before 45 years of age
AND
First- or second-degree relative with a LFS cancer (sarcoma, breast cancer, brain tumor, adrenocortical tumor, or leukemia) at any age
AND
First- or second-degree relative with any cancer under the age of 60

LFS is a highly penetrant cancer syndrome. A segregation analysis conducted on families with LFS revealed 50% increased chance to develop a tumor before 40-year old, compared to 1% of the general population. It has also demonstrated that 90% of the carriers might present a tumor at the age of 60.[10] Cancer patients in these families who survive the first neoplasm are prone to develop second cancers, particularly within the field of radiation therapy. The most common childhood cancers have been soft-tissue sarcomas in the first 5 years of life and osteosarcomas in adolescence. Acute leukemia and brain tumors also occur throughout childhood and young adulthood, whereas adrenocortical carcinomas occur primarily in infancy. In young adults, premenopausal breast cancer is, by far, the most common neoplasm.[5] Clinically, the entire range of cancers in the syndrome remains to be defined.

Table 3 - Clinical criteria for Li-Fraumeni Like syndrome (Eeles)

Eeles 1
Two different tumors that are part of extended LFS in first or second degree relatives at any age (sarcoma, breast cancer, brain tumor, leukemia, adrenocortical tumor, melanoma, prostate cancer, pancreatic cancer);
Eeles 2
Sarcoma at any age in the proband AND two of the following: (may be in the same individual)
Breast cancer at <50 years and / or brain tumor, leukemia, adrenocortical tumor, melanoma, prostate cancer, pancreatic cancer at <60 years or sarcoma at any age

The molecular basis of this familial alteration remained unknown until its connection to the *TP53* tumor suppressor gene. In 1990, five families who received a clinical diagnosis of the Li-Fraumeni syndrome were reported to show germline mutations in the *TP53* tumor suppressor gene.[11] Subsequent studies have found germline *TP53* mutations in many, but not all, Li-Fraumeni families.[12] The mutations typically cluster in sequences that code for the DNA binding domain of the p53 protein (see below). These sequences are also the most frequent sites for somatic *TP53* mutations in sporadic cancers. Failure to detect *TP53* mutations in some families with LFS could be due in part to the fact that mutations may occur outside the coding, "hotspot" regions, thus

escaping detection by standard methods. Another explanation is that the syndrome is genetically heterogeneous, with *TP53* mutations accounting for only a fraction of Li-Fraumeni families. Recent data show that 70% of LFS families are attributable to germline mutations in *TP53,* whereas 20% of LFL had a mutation detected.[13] So far 280 families have been identified as carriers of germline p53 mutations.[14,15] Despite intensive search, no other gene has been hitherto associated with LFS / LFL. Earlier reports that the *CHK2* gene may carry germline mutations have not been substantiated. These mutations are now considered as common polymorphisms that may be associated with predisposition to breast cancer.

THE *TP53* GENE

The *TP53* tumor suppressor gene (chromosome 17p13; OMIM#191170) encodes a ubiquitous phosphoprotein involved in many overlapping cellular pathways that control cell proliferation and homeostasis, such as cell cycle, apoptosis, and DNA repair. The coding sequence contains five regions showing a high degree of conservation in vertebrates, and comprises 10 coding exons.[16] The gene contains a very long 5' region containing a non-coding exon 1 and intron 1 over about 10 kilobase pairs. *TP53* mutations appear to be an important alteration in the complex process of carcinogenesis being the most common site of somatic mutations in human cancers. Somatic *TP53* genetic alterations are frequent in a variety of human sporadic cancers, with frequencies varying from 10% to 60%, depending on the tumor type or population group. They are particularly frequent in cancers associated with exposure to environmental or occupational carcinogens (e.g. lung cancers in smokers, bladder cancers in exposed industry workers, among other events). Overall, the types and distribution of germline and somatic *TP53* mutations are very similar, with a majority of missense mutations in the DNA-binding domain encoded by exons 4 to 9 of the *TP53* gene.[17] Splice-site mutations, large deletions and complex insertion-deletion may also be found.[18,19] When present in the germline, *TP53* mutation is considered a first-hit in Knudson's two-mutation model of hereditary cancer development. However, the fate of the remaining, wild-type allele during tumor development is poorly understood. In some instances, this wild-type allele is lost or mutated in cancers, fulfilling Knudson's paradigm. In other cases, this allele persists, but its biological activity seems to be extinguished, perhaps as the result of overexpression and stabilization of the product of the mutant allele. This hypothesis is supported by biological evidence showing that accumulation of mutant p53 protein can inactivate wild-type p53 in a dominant-negative manner. There is emerging evidence that the nature and position of the germline mutation in *TP53* may, to some degree, determine cancer phenotypes in affected carriers. For example, mutations in a specific region of the DNA binding domain encoding protein loops in direct contact with DNA seems to carry a significantly higher predisposition to brain cancers. In contrast, mutations that predispose to adrenal cortical tumors are frequently located outside of the major "hotspots" area. Moreover, it is most likely that other, still unknown genes may act as modifiers, explaining the variations in tumor patterns.

Recently, a specific germline mutation falling into exon 10, encoding the oligomerization domain of p53, R337H (CGC to CAC at codon 337), has been reported in Brazilian children with ADR but no documented familial history of other cancers.[20,21] Structural and functional studies have identified that R337H mutant proteins had a pH-dependent defect in the oligomerization domain, making them inactive only in conditions of increased intracellular pH. It was postulated that arginine 337 is located in the dimerization motif of the p53 protein. Its replacement by histidine alters hydrogen bonding between two p53 monomers and hampers dimerization in a pH-dependent manner. At pH 7, the histidine is protonated and participates in hydrogen bonding. At pH 8, however, the histidine is deprotonated, preventing formation of the hydrogen bond.[22] This would result in disruption of p53 oligomers and inactivation of its binding ability capacity to bind with high affinity to p53-response elements in the regulatory regions of p53-target genes. The unusual prevalence of this mutation in Brazilian families appears to be due to a founder effect.

This observation has led to the speculation that R337H may predispose to cancer development only in tissues in which a rise in intracellular pH is a major growth or survival regulatory signal. Such a rise in pH occurs in apoptotic cells and may play a role in the extensive tissue remodeling that occurs through selective apoptosis in adrenal cortical glands during pre- and post-natal development. It was postulated that this conditional mutant might only predispose to a narrow spectrum of cancers within the LFS spectrum. However, so far no studies have reported whether this mutant is also present in families that match LFS or LFL definitions. Interestingly, the same mutant has been described in a British family matching LFS/LF criteria.

Over 15 polymorphisms are identified in human population, with allele frequencies that vary with ethnic origin.[23] One of them affects the coding sequence at codon 72, specifying either an arginine or a proline. The Arg allele is the most common in the western population (allele frequencies ranging from 0.6 to 0.8) but the prevalence of the Pro allele seems to increase according to a North-South gradient, so that the Pro allele is the most frequent one near the equator and in indigenous populations of the Southern hemisphere.[24] Increasing evidence states that this polymorphism may have a functional impact on cancer susceptibility and response to therapy.[25] Two genes related to *TP53* have been identified on chromosome 1p36 (*TP73*, OMIM 601990) and on chromosome 3p28 (*TP63*, OMIM 603273). Both genes encode proteins with high homology to p53 in terms of overall structure.[26] To date, no association has been found between these genes and familial cancer.

P53 PROTEIN

After 25 years since first described, the p53 protein has been shown to play a key role in both tumor suppression and aging and it has been one of the main targets on molecular cancer research. The p53 protein is a transcription factor constitutively expressed in most cell types and tissues and activated in response to various stress signals, in particular genotoxic stress. Due to its rapid turnover (5-20 minutes) the protein does not accumulate unless it is stabilized in response to a variety of intracellular and extracellular stimuli.

Signals that activate p53 include diverse types of DNA damage (strand breaks, bulky adducts, oxidation of bases), blockade of RNA elongation, hypoxia, depletion of microtubules, ribonucleotides or growth factors, modulation of cell adhesion and alteration of polyamine metabolism.[27] Oncogenic, genotoxic, and non-genotoxic stress interact with main p53 co-factors. The main regulator of p53 protein activity is Mdm-2, a transcriptional target of p53. The p53/Mdm-2 complex is regulated by $p14^{Arf}$ (Alternative Reading Frame), a 14 kD protein encoded by an alternative reading frame of *CDKN2A*, the gene that encodes the

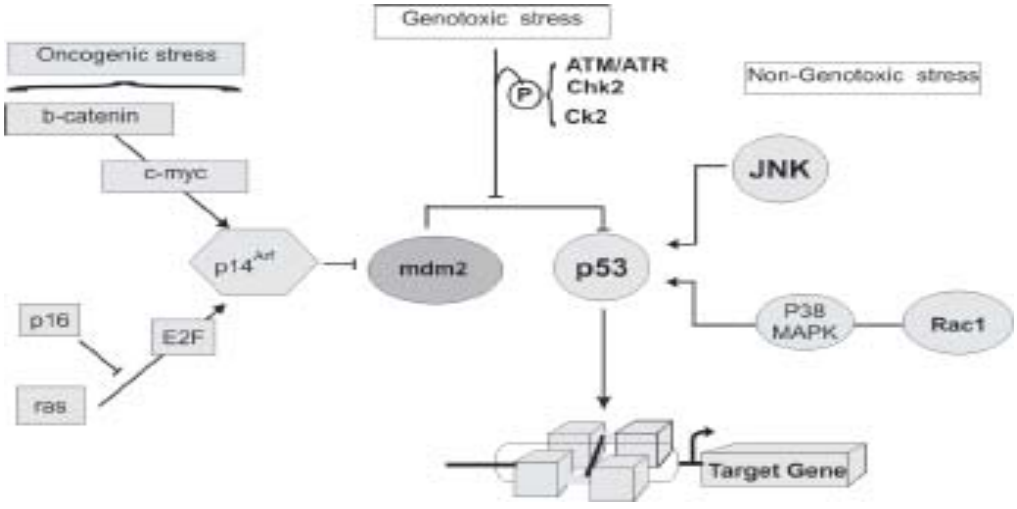

Figure 1 - Pathways of p53 activation

tumor suppressor *p16* (Figure 1).

Once activated, p53 exerts its effects through two major mechanisms: transcriptional control (activation or repression of specific genes) and interference with the function of other protein through complex formation. Over 4800 genes have been identified as containing a p53-response element in regulatory regions.[28] At the cellular level, activation of p53 generally induces either cell-cycle arrest (mostly in G1 and/or G2/M) or apoptosis. However, it must be realized that apoptosis is the preferential response in primary cells and that when cell-cycle arrest is induced, it is generally a permanent one, followed by cell senescence.[29] In other words, activation of p53 in a normal cell generally results in its permanent deletion from the pool of cells with proliferative capacity, providing a drastic way for suppressing any cell that carries a risk of oncogenic transformation.

These functional and biological features provide a rationale to understand the consequences of inheritance of a germline *TP53* mutation. Subjects with only one functional *TP53* allele are at high risk of developing multiple cancers when the remaining allele becomes inactivated by various mechanisms. Loss of p53 function would then create a form of "mutator phenotype", allowing cells to replicate damaged DNA and accelerating their progression towards cancer.

SURVEILLANCE

Both patients with clinical diagnosis of LFS/LFL and *TP53* carriers should be advised to seek early medical attention for signs and symptoms of cancer. There are no established surveillance measures or widely agreed guidelines for mutation screening and management of LFS/LFL patients but surveillance strategies have been suggested for individuals at risk.[30] Patients should be aware of the limitations of screening for many cancers associated with the syndrome. Breast cancer is the most common tumor found in women with LFL/LFS and breast monitoring has been shown to be effective in reducing morbidity or mortality among individuals at risk. Training and education in breast self-exam should be addressed at age 18. Regular semiannual clinical breast exams should be performed starting at age 20 to 25, or 10 years before the earliest known breast cancer in the family; or yearly since younger age. Routine annual mammograms and mammary ultrasounds should begin in women over age 25 years, but have not been proven to be beneficial for younger women with LFS/LFL.[31] Controversy exists regarding the use of routine mammograms because of possible radiation sensitivity associated with *TP53* mutations.[32] A specialist on a case-by-case basis should address other investigational breast imaging possibilities such as MRI, as wells as shorter intervals.

Furthermore, LFS/LFL patients and their possible carriers must receive targeted surveillance based on individual family histories. Due to the multitude of tumors that are included in the syndrome, patients should be educated regarding signs and symptoms of cancer and complaints should be thoroughly investigated. Annual comprehensive physical exam starting in younger adults with suspicion for rare tumors and second malignancies in cancer survivors should be addressed. Additional organ-targeted surveillance based on family history is of great value, such as colonoscopies at regular intervals if a relative has had colorectal cancer. Full-body MRI examination or PET scan has been suggested. However, no evidence supporting the benefit of such testing exists and it is possible that it may lead to unnecessary biopsies or other follow-up tests. Perhaps most importantly, at-risk individuals and their physicians are urged to pay greater attention to lingering symptoms and illnesses, particularly headaches, bone pain, or abdominal discomfort, and to schedule diagnostic tests promptly.

Patients should receive genetic counseling and advice about risk to relatives and possibility of genetic testing. In 1992, an International Consortium of clinicians and researchers convened and developed recommendations regarding genetic testing for germline *TP53* mutations.[6] These recommendations state that testing should be done voluntarily with appropriate pre- and post-test.

For at-risk children, pediatricians should be warned about the syndrome and apprised of the risk of childhood cancer in affected families. They must be evaluated on annual complete physical examination and an additional

organ-targeted surveillance based on family history should be considered.[30]

Individuals with *TP53* mutations should avoid or minimize exposure to radiation whenever possible.[33] The *TP53* gene is recognized as playing a crucial role in genomic repair.[34] *TP53*-deficient mice are prone to early formation of multiple, spontaneous cancers and p53-deficient mouse cells have been shown to be radiation sensitive and prone to cancer.[35] Radiation-induced second malignancies have been reported among individuals with *TP53* mutations.[36-38] A high incidence of exposure to genotoxic agents, such as to pesticides, has been reported in some families but to date, no correlation has been established.[17]

Conclusion

After 25 years of research and over 30 000 publications, studies on *TP53* have had a major impact on our understanding on cancer molecular biology . The challenge for the years to come is to turn this knowledge into advances in cancer prevention, detection, prognosis and therapy. New discoveries about the function and control of p53 continue to emerge every month and attempts to exploit the system to develop better therapeutics and diagnostics are beginning to be successful in clinics. Current understanding of LiFraumeni syndrome and its association with germline *p53* mutations is incomplete. Additional studies are needed for cancer spectrum in the syndrome, the role of environmental carcinogens in cancer development among family members, possible genetic heterogeneity and other methods, age-specific penetrance of the mutant gene, and rare p53 polymorphisms that might be mistaken for functional mutations.

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