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p53 REVIEW ARTICLE

TP53 Mutations in Familial Breast Cancer: Functional Aspects

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For the p53 Special Issue

Mutation in p53 (TP53) remains one of the most commonly described genetic events in human neoplasia. The occurrence of mutations is somewhat less common in sporadic breast carcinomas than in other cancers, with an overall frequency of about 20%. There is, however, evidence that p53 is mutated at a significantly higher frequency in breast carcinomas arising in carriers of germ-line *BRCA1* and *BRCA2* mutations. Some of the p53 mutants identified in *BRCA1* and *BRCA2* mutation carriers are either previously undescribed or infrequently reported in sporadic human cancers. Functional characterization of such mutants in various systems has revealed that they frequently possess properties not commonly associated with those occurring in sporadic cases: they retain apoptosis-inducing, transactivating, and growth-inhibitory activities similar to the wild-type protein, yet are compromised for transformation suppression and also possess an independent transforming phenotype. The occurrence of such mutants in familial breast cancer implies the operation of distinct selective pressures during tumorigenesis in BRCA-associated breast cancers. Hum Mutat 21:301–306, 2003.

KEY WORDS: breast cancer; cancer; tumor; p53; TP53; BRCA1; BRCA2; transactivation; apoptosis; Li-Fraumeni syndrome; LFS

DATABASES:
TP53 – OMIM: 191170, 151623 (LFS); GenBank: NM_000546 (mRNA)
http://p53.curie.fr/ (p53 Web Site at Institut Curie)
www.iarc.fr/p53 (IARC p53 Mutation Database)
BRCA1 – OMIM: 113705; GenBank: U14680
BRCA2 – OMIM: 600185; GenBank: U43746

INTRODUCTION

The p53 gene (TP53; MIM# 191170) is one of the most commonly mutated genes thus far described in human neoplasia, with mutations estimated to occur in up to 50% of all cancers. Mutations are principally, but not exclusively, missense. The majority of mutant proteins are defective for sequence-specific DNA binding and transactivation of p53-responsive genes, and some have acquired dominant transforming activity [Ko and Prives, 1996; Sigal and Rotter, 2000].

The status of p53 in human breast cancer has been the subject of intensive investigation [reviewed in Gasco et al., 2002; Borresen-Dale, 2003]. The presence of mutation, with or without accompanying loss of heterozygosity (LOH), was an early finding in cell lines and primary breast cancers, establishing p53 as a bona fide tumor suppressor gene in the breast. Breast carcinomas are also a recognized clinical feature in Li Fraumeni syndrome (LFS; MIM# 151623), in which germ-line carriage of p53 mutation predisposes to an increased incidence of several cancers. However, whereas p53 is mutated at a high frequency in several common human solid tumors, the frequency of mutation in sporadic breast cancer is substantially lower [Pharoah et al., 1999]. Specific forms of the disease appear, however, to be associated with a higher frequency of p53 mutations. These include cancers arising in germ-line carriers of *BRCA1* (MIM# 113705) and *BRCA2* (MIM# 600185) mutations and typical medullary breast cancers, which share a number of pathobiological features with *BRCA1*-associated cases [de Cremoux et al., 1999].

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BRCA1/BRCA2 INSUFFICIENCY MAY ACTIVATE TP53-DEPENDENT CHECKPOINTS

Germ-line mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2* confer a substantially increased risk of breast cancer [Miki et al., 1994; Wooster et al., 1995]. Following the cloning of *BRCA1*, attempts were made to generate knock-out mice. These experiments were unsuccessful, embryonic death occurring before day 7.5 due to growth arrest associated with up-regulation of expression of $p21^{Waf1}$ and down-regulation of mdm2 [Hakem et al., 1996]. Subsequently, it was shown that this phenotype could be partially reversed by crossing into mouse strains carrying null mutations in p53 or $p21^{Waf1}$ [Hakem et al., 1997]. Like *BRCA1* mutant mice, deletion of exons 10 and 11 of *BRCA2* results in death during embryogenesis and this too was shown to be associated with impaired cellular proliferation and up-regulation of $p21^{Waf1}$ [Suzuki et al., 1997]. These studies thus revealed that loss of *BRCA1* and/or *BRCA2* function results in a $p21^{Waf1}$-mediated G1 growth arrest that is, at least in part, p53-dependent. Using conditional knock-out of *BRCA1* it has been shown that breast tumorigenesis following induced loss of *BRCA1* requires a lengthy latent period, but this is significantly reduced when the original line is crossed into a p53 +/– strain [Xu et al., 1999]. Extrapolation of these findings to human breast cancer suggested a simple model of tumorigenesis in which it was hypothesized that loss of the wild-type *BRCA1/2* allele originally present in the cells of carriers of mutant alleles of *BRCA1* and *BRCA2* would activate a p53-dependent checkpoint. Abrogation of this checkpoint could be accomplished by mutation in p53, resulting in expression of a mutant protein lacking the ability to activate the checkpoint.

A DISTINCT SPECTRUM OF TP53 MUTATIONS IN BRCA-ASSOCIATED CANCERS

Sequencing studies of p53 have demonstrated an elevated frequency of mutation in *BRCA1*- and *BRCA2*-associated breast cancers compared to grade-matched sporadic cases [Crook et al., 1998; Gretarsdottir et al., 1998; Phillips et al., 1999]. In some *BRCA1* and *BRCA2* carcinomas several independent p53 mutations were detected, these apparently targeting a single allele in certain cases [Crook et al., 1998]. This is reminiscent of an earlier study of familial breast cancers (of unknown BRCA status), in which p53 was mutated at high frequency and multiple mutations and novel p53 alleles occurred commonly [Glebov et al., 1994]. One study has failed, however, to detect an increased frequency in p53 mutation in *BRCA1* cancers [Schlichtholz et al., 1998]. Studies in ovarian carcinoma have also reported an increased frequency of p53 mutation [Ramus et al., 1999; Zweemer et al., 1999]. Taken together, the increased frequency of p53 mutations generally observed in BRCA-associated cancers is consistent with the mechanistic models adduced from studies of tumorigenesis in *BRCA1* mutant mice.

It is now well recognized that p53 mutations in sporadic human tumors preferentially target specific codons. For example, 28% of such mutations occur in codons 175, 245, 248, 249, 273, and 282 [Vousden and Lu, 2002]. Other frequently mutated hot spot codons have also been identified [Walker et al., 1999]. Analysis of breast cancers arising in *BRCA1* and *BRCA2* germ-line mutation carriers revealed that a significant proportion of p53 mutations occurred at non-hot spot codons. Indeed, many mutations were either previously undescribed or very uncommon in human cancer [Crook et al., 1998]. A meticulous review of the p53 mutations reported in the literature has confirmed this and further identified some intriguing and provocative conclusions [Greenblatt et al., 2001]. First, of 73 mutations identified in *BRCA1/BRCA2* mutation carriers no less than 19 had not been previously reported in breast cancer and nine had never been described in any human cancer in the IARC human p53 database (www.iarc.fr/p53/Homepage.htm). Second, in contrast to most of the commonly detected human tumor-associated p53 mutations, the novel non-hot spot mutations detected in the BRCA-associated cancers are located on the non-DNA binding side of p53. The occurrence of CC>TT mutations at dipyrimidine sites in two BRCA-associated breast cancers was another surprising finding in view of the rarity of such tandem mutations in human cancer. Almost all (51/57) previously described CC>TT mutations are in skin cancer where they arise due to aberrant repair of cyclobutane photoproducts. Of the six CC>TT mutations which were detected in other cancers, five are in breast or ovarian cancers, raising the possibility that these may also have occurred in *BRCA1/BRCA2* mutant cancers [Greenblatt et al., 2001]. Together, the frequency and spectrum of p53 mutations identified in these cancers supports the theory that loss of *BRCA1/BRCA2* DNA repair function facilitates the generation (and perhaps selection) of somatic mutations which contribute to tumorigenesis in the breast. A summary of the structural properties of p53 mutations in *BRCA1*- and *BRCA2*-associated cancers is shown in Table 1 [Greenblatt et al., 2001].

TRANSACTIVATING PROPERTIES OF BRCA-ASSOCIATED TP53 MUTANTS

The apparent concentration of previously undescribed and/or extremely rare p53 mutants in

TABLE 1. TP53 Mutation Spectrum in BRCA1- and BRCA2-Related and Sporadic Breast Carcinomas

Mutation type	BRCA1- and BRCA2-related	IARC database
Hotspot	67%	82%
Silent	13%	1%
A:T base pairs	38%	25%
Tandem CC > TT	2%	0.1%
Multiple substitutions	16%	4%

Data derived from Greenblatt et al. [2001].

independent series of BRCA-associated breast cancers clearly merited their functional characterization. One of the most important activities of wild-type p53 is its ability to activate expression of downstream genes via sequence-specific DNA binding and thereby to modulate cellular responses such as apoptosis and cell cycle arrest [Vogelstein et al., 2001]. In an initial study, transactivating activity of the BRCA-associated mutants was analyzed by over-expression in human Saos-2 p53 –/– cells [Smith et al., 1999]. These studies revealed that mutants which occurred at recognized human tumor hot spots (158H, 163N, 168Y, 234C, and 248W) were significantly compromised for sequence-specific DNA binding and transactivating activity (Table 2). These findings were unsurprising, since loss of this activity is common to the vast majority of human tumor-associated mutants. Abrogation of $p21^{Waf1}$ inducing activity also supported the model suggested by studies of *BRCA1* mutant mice in which *BRCA1* loss caused $p21^{Waf1}$ dependent proliferation block. In contrast to the hot spot mutants, however, a significant proportion of non-hot spot mutants retained transactivating activity close to that of the wild-type protein. In particular three mutants, 150I, 199R, and 202S, were virtually indistinguishable from wild-type p53 in assays of transactivation of multiple promoters, including $p21^{Waf1}$ and the apoptosis-promoting genes *Bax* and *PIG3*. This was an unexpected result, since previously described "transactivation competent" mutants such as 175P and 181L are able to activate expression of genes such as $p21^{Waf1}$ but are defective in activation of apoptosis-inducing genes such as *Bax* [Crook et al., 1994; Rowan et al., 1996]. Other BRCA-associated mutants, for example 181C and 215C, also retain wild-type activity in transactivation of some promoters such as *PIG3* (Table 2), but are defective for transactivation of others such as *Bax* and IGF BP3 Box A [Smith et al., 1999]. The properties of these BRCA-associated p53 mutants were further examined in yeast assays by Campomenosi et al. [2001]. In these studies, yeast strains were used which contained an ADE gene whose promoter was regulated by the p53 responsive elements from the $p21^{Waf1}$, *PIG3*, and *Bax* genes. Consistent with the earlier of work of Smith et al. [1999], the incidence of transcriptionally active mutants is significantly higher than in a panel of mutants derived from sporadic human tumors. Furthermore, the incidence of fully transcriptionally inactive mutants is significantly lower than in the sporadic mutants: only 163N, 168Y, and 248W are totally inactive with all promoters under all conditions, whereas each of the remaining 10 mutants show some promoter activation in at least one strain [Campomenosi et al., 2001]. The activity exhibited by 150I, 199R, 202S, and 215C was indistinguishable from wild-type p53 in each of the yeast reporter strains, consistent with analyses performed in human cells [Smith et al., 1999].

Activation of $p21^{Waf1}$ correlates well with p53-dependent inhibition of proliferation of p53 null cells such as Saos-2 and each of the BRCA-associated mutants with wild-type or close to wild-type ability to transactivate $p21^{Waf1}$ efficiently suppressed Saos-2 growth [Smith et al., 1999]. The only exception to

TABLE 2. Properties of TP53 Mutants from BRCA1- and BRCA2-Associated Breast Carcinomas

Mutant	Hotspot	p21[a]	p21[b]	PIG3[c]	PIG3[d]	Apoptosis[e]	Transformation[f]
Wild-type	N/A	+++	+	+++	+	+++	–
144P	No	–	–	–	–	–	++
150I	No	+	+	+++	+	+++	+
158H	Yes	+	+/–	–	–	+	++
163N	Yes	–	–	–	–	–	+++
168Y	Yes	–	–	–	–	–	+++
181C	Yes	+++	+	+++	–	++	+
199R	No	+++	+	+++	+	+++	+
202S	No	+++	+	+++	+	+++	+
215C	Yes	+++	+	+++	+	++	+
219H	No	+	+/–	+	+/–	–	++
248W	Yes	–	–	–	–	–	+++

[a]Transactivation determined in Saos-2 human cells: +, 20–50% of wild-type; +++, 50–100% of wild-type.
[b]Results from yeast-based assay. + white colonies; +/–, pink colonies; –, red colonies. Results shown are from growth at 37°C.
[c]Determined in Saos-2 cells.
[d]Yeast-based assay.
[e]Determined in Saos-2 cells. +, 10–20% of wild-type; ++, 20–50% of wild-type; +++, 50– 100% wild-type.
[f]Determined in primary rat embryo fibroblasts by co-transfection with activated *ras*. +, 10–20% of positive control (173L); ++, 20–50% positive control.

this correlation was mutant 144P, which lacks detectable ability to activate $p21^{Waf1}$, yet was nevertheless shown to inhibit Saos-2 by 40–50%.

APOPTOSIS

Loss of apoptosis-inducing activity is a property common to virtually all previously characterized human tumor-associated p53 mutants [Ko and Prives, 1996]. The hot spot BRCA-associated mutants 158H, 163N, 168Y, and 248W, together with two non-hot spot mutants 144P and 219H have only minimal activity in assays of p53-dependent apoptosis assessed by over-expression in Saos-2 cells (Table 2). In contrast, mutants 150I, 199R, and 202S possess close to wild-type activity, while 181C and 215C also retain significant activity. Retention of apoptosis-inducing activity by a significant proportion of the BRCA-associated mutants is another unexpected finding, but closely parallels their transactivating profiles.

TRANSDOMINANCE AND TRANSFORMATION

Certain p53 mutants can trans-dominantly inhibit wild-type p53 when the two forms of the protein are co-expressed in the same cell. Examples of such mutants include 245C, 248W, and 273H [Aurelio et al., 2000]. Analysis in yeast of the *BRCA1*- and *BRCA2*-associated p53 mutants for their ability to inhibit wild-type p53 revealed that only the hot spot mutants 163N, 168Y, and 248W efficiently inhibit p53-dependent transactivation of *Bax*. All the mutants that behaved like wild-type p53 in transactivation assays were always recessive to wild-type p53 [Monti et al., 2002]. The inability of these mutants to inhibit wild-type p53 is interesting since these same mutants all possess some independent transforming activity in primary rodent cells. As such, these results imply that transdominant inhibition of endogenous p53 may not be an absolute requirement for in vitro transforming activity. A similar conclusion was reached in earlier analysis of mutants 175P and 181L, which have transforming phenotypes yet are recessive to wild-type p53 [Crook et al., 1994]. It should be noted, however, that the most potent transforming mutants from the BRCA-associated cancers, namely 163N, 168Y, and 248W, are those which are dominant to p53 [Smith et al., 1999; Monti et al., 2002]. One of the properties of wild-type p53 is its ability to suppress in vitro transformation mediated by co-operating oncogenes such as E1A and *ras* [Finlay et al., 1989]. This activity is absent from each of the BRCA-associated p53 proteins, supporting their status as genuine mutants, although the functional defect responsible for this cannot be definitively identified from the presently available data [Smith et al., 1999].

CONCLUSIONS

Transactivation-competent p53 proteins comprise only about 20% of all detected mutants in human cancers [Campomenosi et al., 2001]. However, whereas such mutants are able to activate the promoters of non-apoptotic genes such as $p21^{Waf1}$, they are invariably unable to activate expression of apoptotic genes and, like virtually all human tumor-associated mutants, are compromised for apoptosis induction [Crook et al., 1994; Rowan et al., 1996; Campomenosi et al., 2001]. The occurrence of apparently fully transactivation- and apoptosis-competent mutants in *BRCA1*- and *BRCA2*-associated breast cancers is therefore most unexpected and raises the questions: What is the mechanistic basis for their selection in cancer and why is their presence in human cancer restricted to BRCA-associated cases?

One obvious possible answer to the first question is that the mutants are compromised in their ability to transactivate genes whose p53-responsive elements have not yet been functionally tested. The promoters of p53-responsive genes exhibit considerable heterogeneity with respect to their inducibility by wild-type p53. Furthermore, p53 target genes whose transcriptional regulatory elements contain low-affinity p53 binding sites may require additional events for activation [Szak et al., 2001]. Models of p53 action propose that the promoters of apoptotic genes are generally of lower affinity than those of genes such as $p21^{Waf1}$, which function in cell-cycle arrest. Numerous effector proteins of p53-dependent apoptosis such as p53*AIP*1, *PUMA*, *Apaf*1, *NOXA* have been described [Vousden and Lu, 2002] but the inducibility of these by BRCA-associated p53 mutants has not been determined. It is therefore an interesting possibility that the apparently wild-type BRCA-associated mutants are in fact functionally compromised for activation of other p53-responsive genes. Recent evidence shows that this may indeed be the case. Testing of the mutants in a panel of yeast strains containing p53-responsive elements from a large number of p53-inducible genes has revealed subtle transactivating defects in each of the mutants previously considered to have a fully wild-type transactivating phenotype [Inga et al., 2002]. Further characterization of multiple p53-responsive promoters in such systems will clearly be of considerable interest and may allow identification of p53-inducible genes functioning in transformation suppression. Another interesting and perhaps related possibility is that the BRCA-associated p53 mutants are compromised in their ability to interact with transcriptional co-activators of p53. Again, there is preliminary evidence to support this possibility. The ASPP family of proteins (apoptosis-stimulating proteins of p53) selectively activate the apoptosis-inducing function of p53

[Samuels-Lev et al., 2001]. Amino acid 181 of p53 is involved in protein–protein interaction with ASPP1 and the 181C mutant detected in two cases of BRCA-associated breast cancer binds less efficiently to ASPP1 than wild-type p53. The 181C protein is, therefore, insensitive to the apoptosis-promoting effects of the ASPP proteins suggesting a potential mechanism for selection of 181C in BRCA-associated cancers.

It is worth pointing out that apoptosis-inducing activity of the BRCA-associated mutants was determined in our original studies simply by transient over-expression of p53 protein from CMV-based eukaryotic expression vectors in Saos-2 cells [Smith et al., 1999]. The effect of p53-activating stimuli such as DNA damage, hypoxia, and deregulated E2F on the apoptosis-inducing function of the mutants was not, therefore, assessed. More recent studies in breast cells engineered to inducibly express some of the mutants originally designated as having fully wild-type properties, has revealed defective apoptosis induction and aberrant phosphorylation in response to specific p53-activating stimuli (unpublished observations). Such systems may therefore be more sensitive and appropriate for the detection of these subtle differences than those utilizing p53 over-expression.

Why then should such distinctive mutants only occur in BRCA-associated cancers? Perhaps the genetic background arising in BRCA null cells allows the selection of p53 mutants possessing properties whose expression cannot be tolerated in cells with intact *BRCA1* (and/or *BRCA2*). One clue may come from the interaction of BRCA1 with wild-type p53. Full-length BRCA1 protein associates with wild-type p53 and is able to increase transcription from p53-dependent promoters such as $p21^{Waf1}$ and *Bax* [Zhang et al., 1998]. Tumor-derived mutants of BRCA1 are defective for transcriptional co-activation of p53, and truncation mutants of BRCA1 retaining the p53 interaction domain can function as dominant–negative inhibitors of p53. In cancers arising in germ-line carriers of BRCA mutations, the co-activating effect of BRCA1 is absent. In this situation, the transactivating activity of mutants such as 150I, 199R, 202S is likely to be attenuated allowing their expression to be tolerated. The subtle functional changes in such mutants, as evidenced by their loss of transformation suppression and gain of independent transforming activity, may then be sufficient to confer selective advantage.

It is an interesting possibility that the BRCA-associated mutants represent the minimal loss of function required to lose p53-dependent tumor suppression. Further detailed characterization and identification of the subtle defects they harbor may provide valuable insights into the functions of p53 mediating suppression of transformation and tumorigenesis.

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