Ciência Rural
ISSN: 0103-8478
cienciarural@mail.ufsm.br
Universidade Federal de Santa Maria
Brasil

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Ciência Rural, vol. 42, núm. 5, mayo, 2012, pp. 845-853
Universidade Federal de Santa Maria
Santa Maria, Brasil

Ciência Rural, Santa Maria, v.42, n.5, p.845-853, mai, 2012
ISSN 0103-8478

P53 gene: major mutations in neoplasias and anticancer gene therapy

Gene p53: principais mutações em neoplasias e terapia gênica anticâncer

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ABSTRACT

The p53 gene encodes a protein that has molecular weight of 53kD and is also called p53 protein, being constantly studied for its classic concept of "genome guardian". This gene plays a range of essential functions to ensure the cell cycle control, in addition to playing a central role in carcinogenesis. With respect to neoplasias, it prevents the neoplastic transformation through three intricate mechanisms. Depending on the extent of the mutation, different responses may be sent by p53 and those range since the disruption of the cell cycle, the correction of the mutation through the activation of repair proteins or still, the induction of senescence or cell death by apoptosis. This review aims to address the structural and functional aspects of the p53 gene and protein, and also reaffirm their participation in the carcinogenesis control, approaching their major mutations and the anticancer gene therapy involving this gene.

Key words: *mutations, neoplasia, gene therapy, p53.*

RESUMO

O gene p53 codifica uma proteína que tem peso molecular de 53kD e é também chamada de proteína p53, sendo constantemente estudado por seu conceito clássico de "guardião do genoma". Esse gene desempenha uma série de funções essenciais para garantir o controle do ciclo celular, além de desempenhar um papel central na carcinogênese. Com relação a neoplasias, impede a transformação neoplásica através de três mecanismos intrincados. Dependendo da extensão da mutação, diferentes respostas podem ser enviadas por p53 desde a ruptura do ciclo celular, a correção da mutação através da ativação de proteínas de reparo ou, ainda, a indução de senescência ou morte celular por apoptose. Esta revisão visa a abordar os aspectos estruturais e funcionais do gene p53 e proteína, e também reafirmar a sua participação no controle da carcinogênese, abordando suas principais mutações e a contribuição para a terapia gênica anticâncer.

Palavras-chave: *mutações, neoplasia, geneterapia, p53.*

INTRODUCTION

Both benign and malignant neoplasias are genetic diseases which mutations that originate them may be transmitted hereditarily by germinative lineage or acquired from somatic tissues (STRICKER & KUMAR, 2008). They are the result of a pleiotropic change of the cellular state from the accumulation of genetic and epigenetic changes that disrupt the regular cellular events (ROSSARI, 2004). The genetic hypothesis of cancer implies that the tumor mass results from the clonal expansion of a progenitor cell that has been injured in certain genes (LINDSTROM & WIMAN, 2002).

The tumors usually arise when a number of mutations involving different genes accumulate in a given tissue (LOBO, 2008). Growth promoter proto-oncogenes, tumor suppressor or growth inhibitor genes, the genes that regulate the programmed cell death and those involved in involved in DNA repair are the major targets of genetic injury. These genes are

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Received 09.19.11 Approved 12.01.11 Returned bay the author 03.20.12
CR-6062

recognized as major molecular determinants of cancer and comprehending the role played by each of these elements is crucial for understanding the neoplastic development, onset and progression (LOBO, 2008; STRICKER & KUMAR, 2008). A schematic representation of the molecular determinants involved in cancer is shown in figure 1.

However, once it is a broad and complex subject, in this work the tumor suppressor genes will be particularly emphasized, with particular highlight to the p53 gene and protein.

DEVELOPMENT

The concept of tumor suppressor genes was first suggested by researcher Alfred Knudson, in 1971, based on observations of children with a rare tumor originating in retinoblasts, called retinoblastoma. Knudson postulated that, for the o onset of a neoplasia, both alleles of a tumor suppressor gene should mutate. Thus, unlike oncogenes, which depend on only one active copy of the gene to express the phenotype (dominant action), the tumor suppressor genes should have both alleles affected to induce cancer, meaning that these genes show recessive behavior (EL-DEIRY, 2003; TESTA & HINO, 2003). Primarily, the tumor suppressor gene expression was assigned to genes involved in the control of strategic points of the chain of events related to cell growth and differentiation, preventing the uncontrolled proliferation of cells (ROTH & SWISHER, 1999). Sequentially, the class of tumor suppressor genes has expanded to include different types of cancer-related genes that, when inactivated, through either genetic and/or epigenetic means, allow uncontrolled cell proliferation with subsequent tumor growth. Accordingly, this terminology does not portray correctly the role of these genes, since they are mainly related to the regulation of cell growth and not directly against the development of tumors (BRASILEIRO FILHO, 2009).

Tumor suppressor genes are divided into two classes, the caretaker genes and the gatekeeper genes, according to the role they play. Caretaker genes are responsible for the processes that ensure the genome integrity and those related to DNA repair. Mutation in these genes does not directly affect cell proliferation and survival, but influences negatively the body´s ability to repair injuries in other genes, as

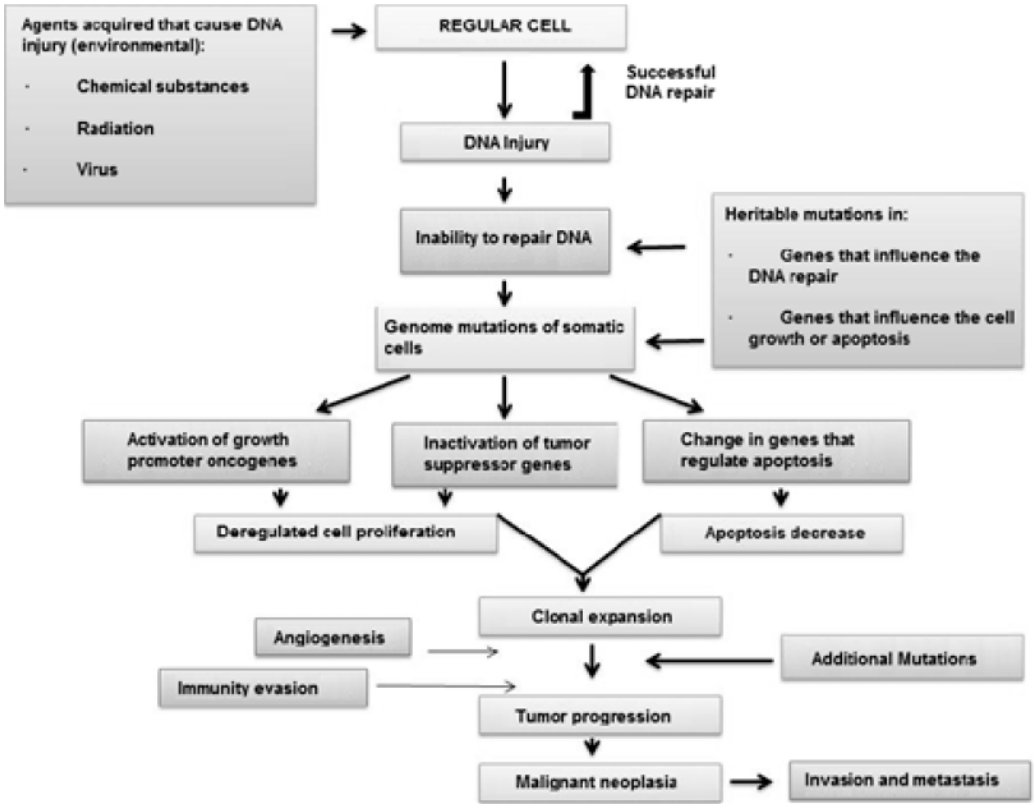

Figure 1 - Simplified flow chart of the molecular basis of neoplasias. Source: STRICKER & KUMAR, 2008.

proto-oncogenes, in genes that regulate apoptosis, as well as in the tumor suppressor genes themselves (BRASILEIRO FILHO, 2009). The consequent inability of the DNA repair genes predisposes cells to mutations throughout the genome and, therefore, neoplastic transformation (STRICKER & KUMAR, 2008). Tumor suppressor genes of the gatekeeper class, or traditional suppressor genes, play the role of controlling cell proliferation (BRASILEIRO FILHO, 2009). RB (retinoblastoma gene) and p53 genes are examples of gatekeeper suppressor genes, and mutations in these genes result in disruption of cell cycle control mechanisms followed by autonomous and uncontrolled proliferation (DURR et al., 2010). p53 is one of the most widely studied tumor suppressor genes, both in medicine and veterinary medicine, once it plays a critical role in cell cycle arrest and apoptosis induction after irreversible damage to DNA (DURR et al., 2010).

p53 gene and protein

The p53 protein history dates from the year 1979, when it was only seen as a tumor suppressor protein. It was first described in cells transformed by SV40 virus (Simian vacuolating virus 40), in which it bound to T antigen (LANE & CRAWFORD, 1979). According to Pierre Hainaut, the p53 gene has broken all theories of definition of a tumor gene. According to the author, "it is not an oncogene, nor an antioncogene, and it may be a mixture of both, but certainly it is an unremitting molecule pursuit the maintenance of the genome integrity" (HAINAUT & HOLLSTEIN, 2000).

The p53 gene is located on the short arm of chromosome 17 (17p13.1). It is a gene composed of 11 exons responsible for encoding a 53kD nuclear phosphoprotein, which contains 393 amino acids, called p53 protein (KERBAUY, 2008). The p53 protein belongs to a small family of proteins, including p63 and p73. It is characterized as a flexible molecule, organized into five structural and functional regions. These regions include the transcriptional activation domain or N-terminal (amino acids 1-44), the regulatory domain rich in proline (amino acids 62-94), the sequence-specific DNA binding domain (amino acids 110-292), the oligomerization domain (amino acids 325-363) and, finally, the multi-functional C terminal domain involved in DNA regulation (amino acids 363-393), (ISOBE, 1986). It is known that the p53 protein has a central hydrophobic globule comprising DNA binding domain flanked by N and C terminal regions (Figure 2). However, the length and full structure of the regular

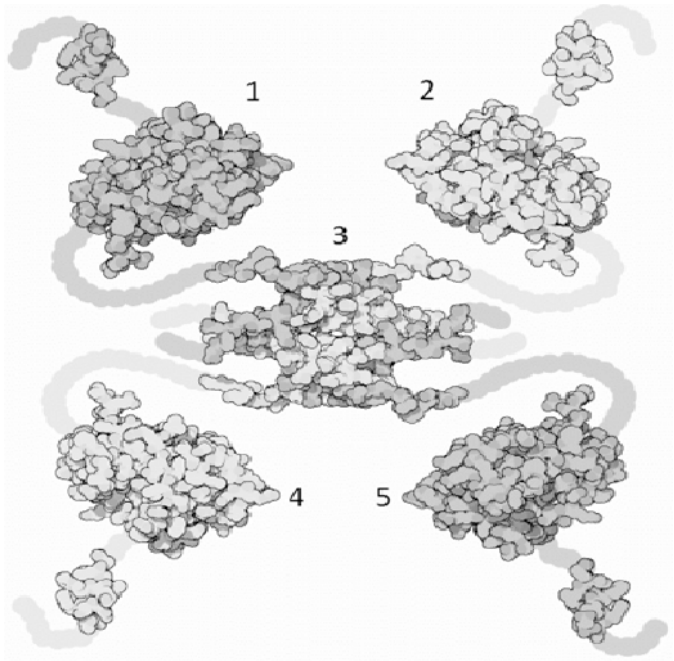

Figure 2 - Representation of the p53 protein molecular structure with the five structural regions. (1) transcription activation domain; (2) regulatory domain rich in proline; (3) sequence-specific DNA domain; (4) oligomerization domain; (5) multi-functional C terminal domain. Source: Adapted from HAINAT & WIMAN (2005).

protein, also known as wild type protein, are not completely clear (HAINAUT & HOLLSTEIN, 2000).

p53 role in the cell cycle

The p53 protein is considered the "genome guardian", since its main role is related to the preservation of the cell genetic code integrity, i.e., maintaining the same sequence of nucleotides along the entire DNA molecule (MCGAVIN & ZACHARY, 2009)

With respect to its role in the cell cycle, HAINAUT & HOLLSTEIN (2000) and KLUMB & CAVALCANTI JÚNIOR (2002) mentioned that this protein acts in different segments, promoting a passive surveillance during all phases of the cycle. Briefly, it is known that the cell cycle is composed of an ordered sequence of phases, as follows: G0, G1, S, G2 and M. The G0 phase is predominant when cells are quiescent, i.e., when there is no stimulus to initiate cell division. In G1 phase, cell stimulated to multiply activates cyclin-dependent kinase genes (CDK), which stimulate cell cycle progression for division and to originate two daughter cells. CDKs activate the gene regulation protein (E2F) which, in turn, activates the transcription of genes responsible for the translation of proteins that lead the cell to the S phase. In this phase, called synthesis phase, there is production of the new DNA molecule, being the new chromosome synthesized with two genetically identical "sister" chromatids. Sequentially, the cycle progresses to G2, phase in which there is the synthesis of RNA and proteins needed for the beginning of cell division or M phase. In M or mitosis phase, there is the cell division itself, forming two daughter cells, identical to the one that originated them (LODISH et al., 2002; WARD, 2002; ALMEIDA et al., 2005).

Acting in cell cycle control, the p53 protein integrates the group of cyclin-dependent kinase inhibitor genes (CDKI), and its primary role is the promotion of CDKs inhibition, leading to the cell cycle evolution disruption (VIALLARD et al., 2001). Additionally, p53 acts in the checkpoints of the cell cycle, i.e., at specific points this protein checks the quality of the cycle progression to ensure that a phase does not begin before the end of the preceding phase, and to confirm the success of the molecular events in every phase. In addition, besides p53 there are other genes and proteins that act in the checkpoints, such as p21, p27 and p57 (PADUA & HANSEN, 2009).

Mechanisms of action of p53 in neoplasias

The p53 protein is highly sensitive and able to detect any mutations in the sequence of the genetic code arising from a range of factors, capturing, among other stimuli, errors in DNA replication, inadequate induction of an oncogene, injury due to ionizing radiation, action of viruses, depletion of ribonucleotides, telomerase erosion, hypoxia and anoxia as shown in figure 3 (VOUSDEN & LU, 2002).

Thus, the p53 protein prevents that mutations are introduced into the genetic material, preventing that regular cells become neoplastic. However, the pathway through which p53 senses the damaged DNA and repairs it is not fully elucidated (MICHAEL & OREN, 2003).

Studies show that the p53 protein acts specifically at G1, G2 and M phases, and that three intricate mechanisms are triggered by p53 aiming to prevent the cellular neoplastic transformation (STRICKER & KUMAR, 2008; PADUA & HANSEN, 2009). Depending on the injury extent to the DNA molecule, p53 may stop temporarily the cycle progress, activating the quiescence mechanism, and may stop it permanently, triggering cellular senescence and, ultimately, the mechanism of programmed cell death or apoptosis (VOUSDEN & LU, 2002; PIETSCH et al., 2006).

Quiescence is considered an essential response to the DNA injury in neoplastic cells. The mechanism of action triggered by p53 when detecting a genetic error in late G1 phase consists of increasing the concentration of its protein levels, which, therefore, leads the transcription of the CDKN1A (p21) gene, 19. These genes prevent the binding of the cyclin-CDK complex responsible for the phosphorylation of the RB gene. The RB gene remains conjugated to E2F gene preventing it to exercise the transcription of genes that are essential for cell cycle progression (VIALLARD et al., 2001; BROOKS & GU, 2003).

The temporary disruption mechanism contributes summarily to the action of repair proteins correcting the reversible injuries. Additionally, p53 also contributes to the repair by activating certain proteins, such as GADD45, which operates directly in the restoration of the conformation of the DNA molecule (PIETSCH et al., 2006). In healthy cells, p53 is conjugated to the MDM2 protein, inhibiting the expression of this tumor suppressor protein for extended periods. Thus, under physiological conditions, the half-life of p53 is short, about 20 minutes (LODISH et al., 2002).

However, during the quiescence period, the half-life of the p53 protein is amplified by the occurrence of post-transcriptional changes that release it from the MDM2 and prevents that it performs its action. When the DNA integrity is restored, a negative feedback mechanism incited by the p53 itself stimulates the

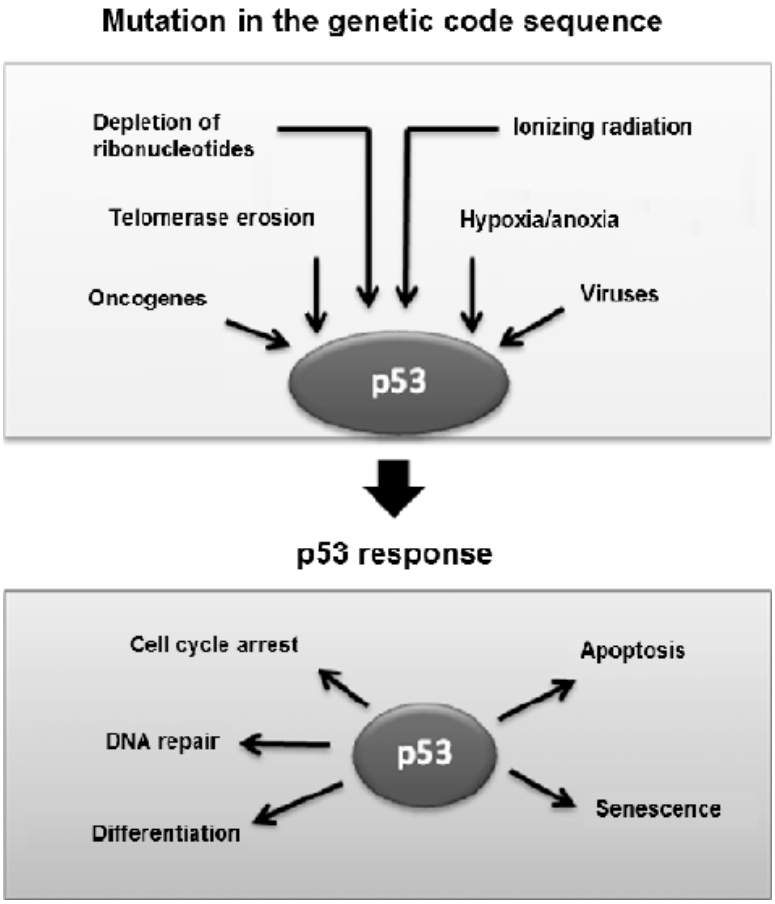

Figure 3 - p53 role in cell cycle. Source: Adapted from VOUSDEN & LU (2002).

transcription of the MDM2 protein to inhibit the p53 expression preventing, therefore, the p21 transcription (MICHAEL & OREN, 2003). Thus, there is a return of the cell cycle progression and the p53 functional excess is restored, minimizing the possibility of protein mutation (LODISH et al., 2002). In many circumstances, the injury persists and thereby the senescence and apoptosis mechanisms are introduced into the molecular environment (PIETSCH et al., 2006).

Senescence induced by p53 is characterized by permanent disruption of the cell cycle through specific changes in cell morphology and expression of different genes. At the end of the process, the cells still have the ability to interact with the environment, but remain permanently in the G1 phase of the cell cycle, not responding to physiologic stimuli for progression in the cycle or for DNA synthesis (LI et al., 2010).

Some studies have shown that senescence may occur at any step of carcinogenesis, although it is more common in pre-neoplastic or non-invasive phases. However, the pathways triggered by p53 that lead to senescence are still uncertain. It is suggested that p53 is responsible for triggering a number of changes in the nuclear chromatin, which would modify drastically and permanently the genetic material expression, resulting in neoplastic cell senescence (PIETSCH et al., 2006; LIN et al., 2010; POST et al., 2010).

The apoptotic stimulus is described as the ultimate mechanism developed by p53 against the neoplastic transformation, although its exact organization is not completely elucidated too (VOUSDEN & LU, 2002; RIVOIRE et al., 2006). It should be noted that although this protein is considered a potent activator of cellular apoptosis, in many cases its response is not capable of generating a full apoptotic stimulus (VOUSDEN, 2000).

According to, JOHNSON et al. (2005) and MOLL et al. (2005), p53 is an important pro-apoptotic gene that prompts apoptosis in cells which are responsive to DNA repair mechanisms. At this point,

cells are induced to apoptosis, primarily by failures in the repair mechanism stimulated via GADD45, as well as by the transcription of other pro-apoptotic genes, via p53, such as BAX (gene of the BCL-2 family associated to the X protein) and PUMA (positive regulator gene of apoptosis) (RIBEIRO et al., 2004). When the pro-apoptotic genes are activated, they secrete perforins and granzymes, cytotoxic mediators that form pores in the mitochondrial membrane of the cell injured, leaving it more susceptible to lysis (CHAIGNI-DELALANDE, et. al, 2006). Studies by DORNELAS et al. (2009) suggested that the prolonged stay of the cell in the G1 phase of the cycle may lead it to apoptosis, and also that the inappropriate output of the G1 phase forces the p53 protein to suppress cell growth more pronouncedly.

Figure 4 shows the important role of p53 in maintaining the genome integrity, acting systematically against injuries to the cell genetic material. Contrary to these determining roles in the homeostasis control, there is the fact that the p53 is a highly unstable gene and frequent target of polymorphisms and mutations that change its conformational structure and prevent that the protein translation occurs in its fullness (STRICKER & KUMER, 2008).

With the loss of the p53 homozygosis, the damage DNA is not repaired and there is marked proliferation of the mutation, genomic instability and loss of important cell cycle control mechanisms, being the cell led to malignant transformation (SÁNCHEZ-SERVÍN et al., 2009). Thus, studies have been developed to understand better the genetic mutations involving the p53 and which, often, support the base of the neoplastic formation and/or complications detected in different neoplastic types (ECKE et al., 2005; FENG et al., 2010; ZHANG et al., 2010).

Major p53 gene mutations

Unlike other tumor suppressor genes that are inactivated by allelic loss, the p53 gene is distinguished by the high frequency of mutations (SÁNCHEZ-SERVÍN et al., 2009). According to STRICKER & KUMAR (2008), the tumor suppressor gene p53 is one of the most commonly involved in different neoplastic processes in human beings and which in over 70% of neoplasias show certain mutation in this gene (MORO et al., 2010)

In general, mutations carry conformational changes in the protein, leading to increased half-life, accumulation in cells and function loss. Mutations may be distributed in two classes, *missense* and *nonsense*. The *missense* mutation, also called polymorphism, is the most common cause of p53 transformation and is characterized by the exchange of one nucleotide in the sequence of pairs of cellular chromosome bases, changing the regular protein role. As a result of punctual mutations, the protein, with its morphofunctional aspects affected, may become inactive or play abnormal roles, such as the loss of responsiveness of the cycle control, inability to promote the activation of DNA repair genes, senescence and cell apoptosis, contributing thus to neoplastic progression (CALAZANS et al., 2010). Also as a result of these changes, p53 is unable to activate the MDM2 protein and, thus, its half-life remains increased (FETT-CONT & SALLES, 2002; ECKE et al., 2005).

The *nonsense* mutation occurs less frequently, due to deletions of gene portions or improper insertion of nucleotides. This type of mutation may lead to a reading interruption in the messenger RNA, changing the protein or exercising the translation of a non-functional protein. In summary, the p53 inactivation by mutation, loss or binding to other proteins results in increased proliferation, genomic instability and loss of cell cycle control mechanisms (KLUMB & CAVALCANTI JÚNIOR, 2002).

Anticancer therapy and p53

The apoptosis and cancer study is beginning to explain why many tumors resist to radiotherapy and chemotherapy. Research reveals that these therapies induce cells to death by apoptosis, once both treatments damage the DNA of neoplastic cells, activating the p53 gene (FISHER, 2001). However, cancer cells that show p53 mutation do not suffer action of this gene, becoming unresponsive to therapies and "immortal" (HAINAT & WIMAN, 2005).

Thus, the gene therapy as a treatment for human diseases has been investigated since early 80´s. The confirmation that inactive or defective genes responsible for certain illness could be replaced by functional genes has revolutionized the base of the antineoplastic therapeutic research (FETT-CONT & SALLES, 2002; LEE et al., 2009).

Conceptually, the treatment of diseases from the transfer of functional genetic material to cells presenting mutated genes, in order to replace or complement these genes responsible for cellular injury is considered gene therapy (FISHER, 2001; LEE et al., 2009). Currently, researchers are studying the gene therapy as a control measure of the resistance of neoplastic cells to apoptosis (TANG et al., 2011; YOSHIOKA et al., 2011). The p53 centrality in neoplastic processes stimulates the search for an anticancer therapy model from this gene (FETT-CONT & SALLES, 2002; ZENG et al., 2011).

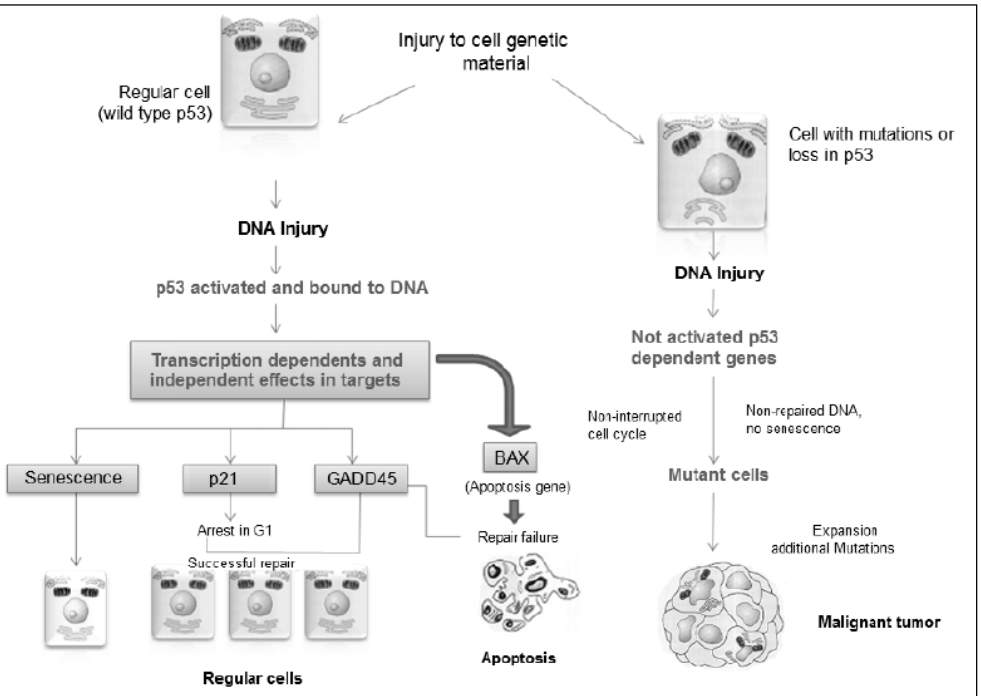

Figure 4 - The p53 role in maintaining the genome integrity. Source: Adapted from STRICKER & KUMAR (2008).

Various strategies can be adopted for discovery of mutant p53 – reactivating compounds (FARNEBO et al., 2010; SCHNEIDER & KRÄMER, 2011; TANG et al., 2011). One of these therapies consists in introducing the p53 gene directly into tumors when there is p53 absence or mutation, to restore the production of the p53 protein in the cell involved (LAU et al., 2008). The gene of interest (also called a transgene) is carried by a vector and is contained in a molecules of DNA or RNA that also carries other genetic elements important for its maintenance and expression (SUNDARARAMAN et al., 2011). The reverse chemical genetics approach is based on screening of chemical libraries for substances that directly affect a target protein. The main advantage is that such screens are focused on a desired biological outcome regardless of mechanism, and that only compounds that are able to enter cells and lack general toxicity are identified (FARNEBO et al., 2010). An inhibitor still experimental, Nutlin-3, showed positive results without causing any side effects to the body. The Nutlin -3 is a small molecule inhibitor, activates p53 by disrupting p53-MDM2 association. The studies demonstrate that Nutlin-3 suppress cell growth and induce apoptosis in the absence of wild-type p53, suggesting a p53 independent mechanism for Nutlin-3 induced cell death (LEE et al., 2009; SONNEMANN et al., 2011). Other studies are devoted to the production of a protein similar to the MDM2, which would act raising the p53 levels indirectly by inhibiting the MDM2. The potential for p53 gene therapy is huge and likely to impact on all aspects of medicine. However, although there is consensus about its promising effect against neoplastic cells, in order that the p53 successful treatment occurs in its fullness, it is also necessary to control the actions of this gene (LAU et al., 2008; LEE et al., 2009).

CONCLUSION

The extensive knowledge about the p53 gene and protein is the starting point for researchers wishing to invest in the molecular biology field, with emphasis on the study of neoplasm. It was possible to notice that the p53 action in the tumor microenvironment is essential to prevent that a regular cell differentiates into a neoplastic cell, thereby becoming an essential gene for maintaining the integrity of life. However, despite its primary role, this small molecule shows many weaknesses, being extremely unstable and in many instances, a constant target of damages and mutations that compromise its

morphologic and functional structure, favoring the installation and dissemination of neoplasias and promoting deleterious effects to the body.

Thus, there is a vast field of research that seeks to elucidate systematically all the points and mechanisms still unclear about the p53, to understand better how to impede the mutations in this gene, preventing that the damage results in uncontrolled cell progression and neoplastic dissemination.

In parallel, research involving gene therapy with p53 or from genes that activate or inhibit its actions constitute a new paradigm in the treatment and prevention of neoplasias, and makes us look for a new inhibition process of cell proliferation. However, data should be analyzed in detail, since drugs with promising effect in preclinical development stage may not be effective in clinical phases.

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