

REVIEW ARTICLE

TP53 Gene Mutation and its Role in the Development of Endometrial Cancer

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Keywords: PT53, genetic mutation, tumor suppressor, endometrial cancer, PI3K/AKT pathway

ABSTRACT

Introduction: The TP53 gene, known as the "guardian of the genome", plays a crucial role in regulating the cell cycle and preventing carcinogenesis. Its mutation is associated with several types of cancer, including endometrial cancer. Alterations in TP53 can compromise DNA repair mechanisms and cellular apoptosis, favouring the uncontrolled proliferation of malignant cells.

Methods: This study is a literature review (2005–2023) on mutations in the TP53 gene present in Endometrial Carcinoma. Studies with techniques such as next-generation sequencing, Real-Time PCR and immunohistochemistry were selected, addressing frequency, risk factors and cellular impact. Clinical trials, reviews and experimental models were included. Specific descriptors and Boolean operators were used to search the scientific databases.

Results: The data analysed indicate that mutations in TP53 are present in a significant proportion of endometrial cancer cases, especially in high-grade tumours. These mutations compromise the function of the p53 protein, allowing cells with DNA damage to avoid apoptosis and continue to proliferate. In addition, tumours with mutations in TP53 are more resistant to conventional treatments, such as chemotherapy and radiotherapy.

Discussion: The presence of TP53 mutations in endometrial cancer reinforces its importance as a prognostic and therapeutic biomarker. Studies suggest that patients with these mutations may benefit from personalised therapeutic approaches, including PI3K/AKT pathway inhibitors and targeted therapies. However, there are still challenges in implementing these strategies, requiring further research to optimise clinical protocols.

Conclusion: Mutations in the TP53 gene play a key role in the progression of endometrial cancer, influencing tumour aggressiveness and response to treatment. Early identification of these mutations may contribute to more effective therapeutic strategies, improving patient clinical outcomes. Future studies should focus on developing targeted therapies for tumours with TP53 mutations, aiming to improve survival and quality of life for patients.

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What do we already know about this topic?

Mutation of the TP53 gene is an important prognostic factor in endometrial cancer, especially in the serous and endometrioid subtypes. Studies indicate that tumors with TP53 mutation tend to be more aggressive, have greater resistance to treatments and are associated with a worse prognosis. In addition, research suggests that the assessment of TP53 mutation may help classify high-risk tumors and guide treatment strategies, such as surgery and adjuvant therapy. Recently, prediction models based on deep learning and radiomics have been developed to estimate the presence of TP53 mutation in patients with endometrial cancer, using diffusion-weighted images. These models have demonstrated high efficacy in identifying the mutation, which may contribute to a more accurate diagnosis and a personalized therapeutic approach. Another study analyzed the clinical and genomic characteristics of endometrial carcinomas with TP53 mutation, revealing that these tumors present specific genetic alterations and distinct survival patterns. Assessment of ERBB2 gene amplification was also recommended for all endometrial carcinomas with TP53 mutation, as it may influence response to treatment.

What is the main contribution to Evidence-Based Practice from this article?

The TP53 gene mutation plays a significant role in the development and prognosis of endometrial cancer, especially in the most aggressive subtypes, such as serous carcinoma. Studies have shown that this mutation is associated with tumors that are more resistant to treatment and worse patient survival. Recently, advances in radiomics and deep learning have made it possible to create predictive models that identify the presence of the TP53 mutation through medical images, allowing for more accurate diagnoses and a personalized therapeutic approach. In addition, the evaluation of the amplification of the ERBB2 gene, frequently associated with tumors with TP53 mutation, may offer new opportunities for targeted treatments. These findings reinforce the importance of genetic analysis in clinical practice, enabling better risk classification of tumors and aiding in therapeutic decision-making for patients with endometrial cancer.

What are this research's implications towards health policy?

The TP53 gene mutation plays a crucial role in theory, clinical practice, and health policies related to endometrial cancer. In theory, this mutation is associated with aggressive tumor progression, providing insights into the molecular mechanisms involved in oncogenesis. Studies on this mutation help to improve understanding of the genetic factors that influence the prognosis of the disease, enabling the development of new tumor classification models. In medical practice, identification of the TP53 mutation can guide therapeutic decisions, allowing physicians to adjust treatment strategies according to the aggressiveness of the tumor. Predictive models based on artificial intelligence have been developed to detect this mutation with greater accuracy, enabling early diagnosis and a personalized approach. In addition, analysis of the amplification of the ERBB2 gene, frequently present in tumors with TP53 mutation, can open new possibilities for targeted therapies, improving clinical outcomes. From a health policy perspective, discoveries about TP53 can influence guidelines aimed at incorporating genetic analysis into endometrial cancer screening and treatment protocols. This can stimulate investment in research on biomarkers and personalized medicine, in addition to promoting public policies that guarantee access to advanced genetic testing for at-risk patients.

Authors' Contributions Statement:

Biazin, Ana Carolyne participated in writing the introduction, results, and discussion of the work. Co-author Berto, Isabela Deungaro participated in writing the results, discussion, and conclusion of the work, Oliveira, Bruno Cateb Resende, participated as Co-author writing the introduction, discussion, methodology, and results of the work.

Introduction

The TP53 gene, located on chromosome 17p13.1, known as the "guardian of the genome", plays an essential role in regulating the cell cycle and preserving genetic integrity. It encodes the p53 protein, which acts to detect DNA damage and activate repair mechanisms or apoptosis, preventing the uncontrolled proliferation of altered cells. However, mutations in this gene can compromise its function, favouring the development of several types of cancer, including endometrial cancer (EC) (Bray et al., 2018).

The EC is one of the most common gynecological neoplasms, and its incidence has increased in recent years. Studies indicate that mutations in TP53 are often associated with more aggressive forms of the disease, such as serous carcinoma, influencing tumour progression and response to treatment. These genetic alterations can result in the loss of the suppressive function of the p53 protein, allowing cells with DNA damage to continue multiplying, contributing to carcinogenesis (Bray et al., 2018).

Given the relevance of TP53 in the development of EC, understanding its mutation

mechanisms and clinical impact is essential to improve diagnostic, prognostic, and treatment strategies. This review seeks to explore the relationship between TP53 mutations and the progression of endometrial cancer, highlighting its implications for medical practice and oncological research (Siegel, Miller, & Jemal, 2019).

The global incidence of EC has been increasing, especially in developed and Western countries, where risk factors such as obesity, sedentary lifestyle, and prolonged exposure to unopposed estrogens contribute to the risk. Mutations in TP53 are most frequently observed in serous endometrial carcinomas, a highly aggressive variant of the disease characterised by rapid growth and increased likelihood of metastasis (Siegel, Miller, & Jemal, 2019) and with a higher incidence among postmenopausal women. In addition, research suggests that the presence of mutations in TP53 may be associated with resistance to certain conventional treatments, such as chemotherapy (CT) and radiotherapy (RT), making clinical management more challenging. Identifying these mutations through genetic testing may be essential for personalising therapeutic strategies, allowing for more effective and targeted approaches (Bray et al., 2018).

The incidence of EC in Brazil has shown significant growth in recent years, reflecting trends observed in developed countries. According to estimates from the National Cancer Institute (INCA), a continued increase in cases is expected until 2025 (Siegel, Miller, & Jemal, 2019).

In Latin America, the incidence of EC varies by country, but tends to be lower than that observed in developed nations. This is due, in part, to differences in dietary patterns, access

to health services, and genetic factors.

However, with the increase in obesity and life expectancy in the region, the incidence is also expected to increase in the coming years (Bray et al., 2018)

In the United States and European countries, the incidence of EC is historically higher. In the US, for example, the rate of new cases is estimated to be over 20 per 100,000 women, with an upward trend due to population ageing and the rise in obesity. In countries such as Germany and the United Kingdom, the incidence is also high, reflecting lifestyles and environmental factors that contribute to the development of the disease (Siegel, Miller, & Jemal, 2019).

Projections indicate that by 2035, the number of EC cases in Brazil could double, in line with the rise in obesity and population ageing. This scenario reinforces the need for public policies aimed at prevention, including awareness campaigns on healthy habits and the importance of early diagnosis (Bray et al., 2018).

Endometrial Cancer

The EC is the sixth most common cancer in women globally (Bray et al., 2018), with an estimated 61,880 new cases and 12,160 deaths in developed countries in 2019 (Siegel et al., 2019). The majority of women diagnosed with EC have early-stage disease and favorable outcomes; this is particularly true for well-differentiated cancers with endometrioid histology (Amant et al., 2005). However, there is a subset of early-stage, low-grade, well-differentiated endometrioid tumors in which unexpected recurrences and poor outcomes occur. Clinical outcomes worsen considerably for women with recurrent or advanced disease and for women diagnosed with a clinically aggressive histologic subtype of disease, such

as serous histotype (Siegel et al., 2018, Walker et al, 2009). EC is one of the few human malignancies with increasing mortality (American Cancer Society, 2017), highlighting the urgent need to develop more effective strategies for the diagnosis and treatment of this disease. The Cancer Genome Atlas (TCGA) recently published a comprehensive genomic study of serous and endometrioid EC and reported four genomic subtypes: POLE, a rare ultramutated subtype with endometrioid histology and good prognosis; microsatellite instability (MSI), a hypermutated endometrioid subtype; low copy number mutation (CNV), which comprises the majority of remaining endometrioid cases; and high CNV, comprising all serous and the most aggressive endometrioid cancers (Kandoth et al., 2013).

TP53

Due to its biological functions, the tumour suppressor p53 is not only an important protector against malignant transformation but can also be used as a prognostic marker in cancer research (Timp & Feinberg, 2013). As a transcription factor, p53 controls the growth of normal cells by coordinating the expression of genes that promote cell cycle progression or cause cell cycle arrest in the G1 phase, especially in cases where the genome is damaged. Furthermore, in response to DNA damage, active p53 is essential for inducing apoptosis in cells that have reached growth arrest (Fisher, 1994). This process is particularly effective when carcinogenic triggers are present. Recent studies have illuminated the intriguingly complex dynamics of p53 signalling, revealing not only its protective role in normal cells but also its paradoxical contributions to cancer pathogenesis when dysregulated. In cancer, TP53 is frequently mutated or expressed at abnormally high

levels, altering the normal regulatory functions of p53 and contributing to tumour progression and aggressiveness (Fisher, 1994). This dichotomy is apparent in a wide range of cancers, such as endometrial carcinoma (Pijnenborg et al., 2006), where TP53 overexpression often predicts adverse outcomes. In this cancer, TP53 status is closely linked to disease progression and significantly impacts patient outcomes. Furthermore, theoretical models (Gao & Chen, 2020) have proposed that p53 dynamics in response to DNA damage, such as oscillatory behaviour driven by transcriptional and translational delays, are crucial for effective DNA repair. These models offer a potential window to therapeutically manipulate p53 pathways to balance its tumour-suppressing capabilities versus its role in cancer promotion (Gao & Chen, 2020).

The fact that p53 is frequently mutated in approximately 50% of human malignancies indicates that p53 plays an important role in triggering cell cycle arrest or progression to apoptosis (Cadwell & Zambetti, 2001; Vogelstein, Lane, & Levine, 2000, Sun et al., 2009). When cells experience DNA damage, such as double-strand breaks (DSBs) caused by ionising radiation (IR) and other pharmaceutical agents, the p53 regulatory network is triggered. This arrests the cell cycle, allowing the cell to repair any damage, triggers transcription of a gene indirectly involved in DNA repair, and triggers apoptosis to eliminate irreversibly damaged cells. Furthermore, Zhang et al. (2009) suggested that the number of p53 pulses could predict the fate of a cell – whether it survives or dies. Furthermore, Chen et al. (2013) and Purvis et al. (2012) suggested that p53 dynamics govern the DNA damage response, deciding the fate of a cell between life and death. This indicates that the

development of cellular control techniques requires a deep understanding of the dynamics of the p53 regulatory network in the DNA damage response. The importance of p53 in cellular responses to genotoxic stimuli is highlighted by evidence suggesting that intact p53 can trigger apoptosis after exposure to IR (Lowe et al., 1994). In contrast, loss of p53 function has been reported to be associated with increased cellular resistance to a variety of chemotherapeutic drugs, highlighting its role in regulating therapeutic responses during cancer treatment.

Previous research has established TP53 as one of the most frequently mutated genes in human cancers, with alterations in p53 function implicated in the initiation and progression of several malignancies. Furthermore, studies have consistently demonstrated an association between TP53 mutations and adverse clinical outcomes, including increased tumour aggressiveness and reduced patient survival. However, despite this wealth of evidence, our understanding of the comprehensive landscape of TP53 mutations and their functional consequences in diverse cancer types remains incomplete (Marei et al., 2021). The p53, a key tumour suppressor gene, orchestrates the delicate balance of the cell cycle by inhibiting uncontrolled cell division. However, elevated p53 expression can tip the balance, promoting the development and aggressive growth of tumours. This phenomenon is attributed to several factors, including exposure to carcinogens, genetic mutations, or viral infections. The scope of p53 overexpression spans a spectrum of cancers. Notably, elevated p53 expression is associated with more aggressive cancers with a higher risk of recurrence. Treatment strategies for tumours that exhibit p53 overexpression often involve a multifaceted approach, combining p53-

targeted therapies with CT, RT, and targeted drug therapies (Marei et al., 2021).

The influence of p53 transcends five distinct pathological stages, each categorised based on the levels of p53 expression in the tumours. Stage I shows minimal p53 expression, while stage V shows the highest levels. Tumours with increased p53 expression often manifest malignant features, with a poorer prognosis. Therapeutic approaches for these cases involve therapies targeting the p53 gene, complemented by CT, RT, and targeted drug therapies (Marei et al., 2021).

The p53 manifests in four distinct subtypes, shaped by mutations or genetic alterations: wild-type, mutant, overexpressed, and deleted. Wild-type represents the normal form of the gene, while mutant, overexpressed, and deleted forms indicate genetic deviations. Each subtype aligns with different cancer types, justifying personalised treatment strategies. For example, mutant p53 is associated with specific lung cancers, suggesting targeted therapies as potential interventions (Marei et al., 2021).

Methodology

This study is a literature review from 2005 to 2023. Scientific databases such as PubMed, Medline, Scopus, and Web of Science were selected to identify relevant studies on TP53 mutations associated with EC. The inclusion criteria were studies that analysed specific mutations of this gene in samples from patients with EC.

To identify these mutations, we used studies that addressed genetic sequencing techniques, mainly next-generation sequencing (NGS), which allows the detection of alterations in the TP53 gene. Studies that also addressed techniques such as Real-Time PCR (qPCR) and immunohistochemistry (IHC), which are commonly used to evaluate p53 protein

expression in tumour tissues, were also included for greater sample specificity. The studies included were clinical trials, studies, reviews, and epidemiological studies to complement the analysis, examining the frequency of mutations in different populations and their associations with risk factors cited in this manuscript. Experimental models, such as cell cultures and animal models, were also used to evaluate the impacts of mutations on cell proliferation and resistance to treatments. The following terms and derived keywords were used: "Carcinoma, Endometrioid", "TP53 gene", "mutation", together with Boolean operators to better approach the studies of interest.

Results

The TP53 encodes the p53 protein, which acts as a tumour suppressor, regulating the cell cycle and preventing the uncontrolled proliferation of cells with DNA damage. When this gene undergoes mutations, its protective function is compromised, allowing altered cells to multiply uncontrollably, favouring tumour progression.

Mutations in TP53 can be somatic or germline, and both have significant impacts on tumorigenesis. Somatic mutations occur throughout life due to environmental factors, such as exposure to radiation, chemical carcinogens, oxidative stress, and chronic inflammation. These mutations are present only in tumour cells and are frequently observed in aggressive cancers, including endometrial serous carcinoma. Germline mutations are genetically inherited and are associated with Li-Fraumeni Syndrome, a rare condition that predisposes individuals to the early development of multiple tumours. These mutations can result in the loss of p53 protein function, preventing it from acting in DNA

repair and inducing apoptosis. In some cases, the mutation can lead to the production of a dysfunctional p53 protein, which is unable to prevent uncontrolled cell proliferation. This allows genetically altered cells to continue multiplying, favouring tumour growth and increasing resistance to conventional treatments.

The EC can be classified into different subtypes, the most common being endometrioid carcinoma and serous carcinoma. Mutations in TP53 are particularly associated with serous carcinoma, which is highly aggressive and has a worse prognosis compared to other types of endometrial cancer.

The main consequences of TP53 mutation in endometrial cancer include genomic instability, where, without the regulatory function of the p53 protein, tumour cells accumulate additional mutations, becoming more aggressive and resistant to treatment. Uncontrolled cell proliferation, where the lack of control over the cell cycle allows tumour cells to multiply rapidly, favours the progression of the disease. Resistance to apoptosis, whereas the mutated p53 loses the ability to induce programmed cell death, altered cells continue to proliferate without restrictions. Increased risk of metastasis, where failure to regulate the cell cycle facilitates the spread of the tumour to other organs.

The identification of TP53 mutations in EC has important implications for diagnosis, prognosis and choice of treatment. Genetic testing can help identify patients with specific mutations, allowing personalised therapeutic approaches. In addition, new strategies are being investigated to restore p53 function, including protein inhibitors that degrade mutated p53 and gene therapies that aim to repair or replace the defective protein.

Protein inhibitors that degrade mutated p53

are a promising approach to restore the function of this tumour suppressor protein in several types of cancer, including EC. The p53 protein plays a crucial role in regulating the cell cycle, detecting DNA damage and inducing apoptosis in cells with irreparable genetic alterations. However, mutations in the TP53 gene can compromise this function, leading to uncontrolled cell proliferation and contributing to tumour progression.

One of the ways in which the p53 protein loses its functional activity is through degradation mediated by regulatory proteins, mainly MDM2 and MDMX. These proteins interact with p53 and promote its degradation, reducing its presence in tumour cells. As a consequence, altered cells are able to escape cellular control mechanisms and continue to multiply, favouring tumour formation and progression. To circumvent this problem, specific inhibitors have been developed, capable of blocking the action of these degrading proteins and allowing the stabilisation of mutated p53.

Among the main compounds studied, Nutlin-3 stands out, an MDM2 inhibitor that prevents its interaction with p53, allowing the protein to accumulate and recover its suppressive function. MDMX inhibitors, which have a similar action to Nutlin-3, but act by specifically blocking MDMX-mediated degradation. APR-246 (Eprexapopt), an innovative compound that not only prevents p53 degradation but also helps restore its functional structure, allowing the protein to recover its normal activity.

The clinical application of these inhibitors is still in the experimental phase, with studies conducted to evaluate their efficacy in tumours resistant to conventional treatment. In preclinical models and initial clinical trials, these compounds have demonstrated potential to improve response to treatment and increase

the sensitivity of tumour cells to apoptosis. Despite the promising advances, there are still challenges to be overcome, such as identifying patients who would benefit most from these therapies, the possibility of tumour resistance, and the long-term safety of these inhibitors. Research in this area continues to advance, to transform these discoveries into effective therapeutic strategies for patients with aggressive and treatment-resistant cancers. Gene therapies represent an innovative and promising approach for the treatment of EC, especially in aggressive tumours associated with mutations in the TP53 gene. TP53 is one of the body's main tumour suppressor genes, encoding the p53 protein, which plays an essential role in regulating the cell cycle, responding to DNA damage, and inducing apoptosis. When this gene undergoes mutations, its protective function is compromised, allowing the uncontrolled proliferation of altered cells and favouring tumour progression.

Gene therapy seeks to restore or compensate for genetic mutations that contribute to the development of cancer. In the case of TP53, one of the most studied strategies is the replacement of the functional gene, in which a healthy copy of the gene is introduced into tumour cells through viral vectors, such as adenovirus or lentivirus. This technique aims to restore the function of the p53 protein, allowing the cell to recover its ability to regulate the cell cycle and induce apoptosis. Another innovative approach involves direct correction of the mutation by gene editing, using technologies such as CRISPR/Cas9, which enables the precise alteration of the mutated DNA, correcting the defect in TP53 and restoring its normal function. This technique has been explored in preclinical studies as an alternative to directly modifying cancer cells,

preventing their uncontrolled proliferation. In addition to gene replacement and correction, some gene therapies focus on modulating proteins associated with p53, such as MDM2 and MDMX, which are negative regulators responsible for the degradation of mutated p53. Inhibitors of these proteins have been investigated to stabilise p53 in the tumour environment, allowing the protein to partially recover its activity and exert its antitumor function. In cases where direct restoration of p53 is not feasible, another therapeutic strategy involves the activation of alternative genes, such as p73, which has functions similar to p53 and can partially compensate for the loss of TP53 activity. Despite the potential of gene therapies in the treatment of EC, there are still challenges to be overcome. Among these are safety and adverse effects, since the introduction of modified genes can generate unexpected immune responses, in addition to the need to improve the efficient delivery of genetic material, ensuring that the vectors reach the target cells without causing side effects. In addition, the possibility of tumour resistance is still a significant obstacle, requiring ongoing studies to perfect these techniques. With the advancement of research, gene therapies are expected to become a viable alternative for the treatment of EC, especially in cases associated with TP53 mutations. Clinical trials continue to investigate new approaches to increase the efficacy and safety of these therapies, allowing more personalised and targeted treatments for patients with aggressive tumours.

Discussion

The TP53 encodes the p53 protein, which acts as a tumour suppressor, regulating the cell cycle and promoting apoptosis of cells with

irreparable DNA damage. When mutated, this gene loses its protective function, allowing altered cells to proliferate uncontrollably, favouring tumour aggressiveness. Mutations in TP53 are strongly associated with endometrial serous carcinoma, a highly aggressive subtype of the disease. These mutations contribute to genomic instability, allowing tumour cells to acquire invasive characteristics and resistance to cellular control mechanisms. In addition, loss of p53 function favours disordered cell proliferation and evasion of apoptosis, making the tumour more difficult to treat.

The presence of mutations in TP53 is correlated with a worse prognosis for patients with EC. Individuals with this mutation have a higher risk of metastasis and a lower survival rate, due to tumour aggressiveness and resistance to conventional treatments. The identification of these mutations through genetic testing may be essential for the personalisation of therapeutic strategies, allowing for more effective and targeted approaches.

The treatment of EC associated with TP53 mutations faces significant challenges, especially due to resistance to CT and RT. As an alternative, new therapeutic strategies are being investigated, such as MDM2 inhibitors, gene therapies and immunotherapy.

The TP53 gene mutation exerts a significant influence on tumour progression in endometrial cancer, directly impacting cell behaviour and response to treatment. TP53 encodes the p53 protein, one of the main regulators of the cell cycle and apoptosis. Under normal conditions, p53 acts as a barrier against the uncontrolled proliferation of damaged cells, preventing tumour formation. However, mutations in this gene compromise this function, leading to cellular alterations that

favour tumour aggressiveness.

The function of TP53 in maintaining genomic stability is crucial to prevent the accumulation of mutations in cells. When there is a mutation in this gene, the natural DNA repair mechanisms fail, allowing tumour cells to accumulate additional mutations and become more resistant to cellular control. This results in accelerated tumour growth, characterised by unbridled cell multiplication and the inability to interrupt the cell cycle when DNA is damaged. Another direct impact is the evasion of apoptosis, one of the body's most important defence mechanisms against cancer. Apoptosis is a process by which defective cells are eliminated in a controlled manner, preventing them from becoming cancerous. However, when p53 is mutated, this mechanism is inhibited, allowing tumour cells to survive and continue to proliferate without restriction. As a result, the tumour grows more aggressively, making it difficult to eradicate it through conventional therapies.

Patients with TP53 mutations often present resistance to CT and RT, as these therapies depend on the activation of apoptosis to eliminate tumour cells. Because the mutated p53 protein fails to trigger this process, tumours become less sensitive to damage induced by treatments. This represents a major clinical challenge, requiring alternative therapeutic strategies that can circumvent this resistance.

In addition to promoting cell proliferation, the TP53 mutation is also associated with an increased metastatic potential of EC. This occurs because the loss of p53 function alters the expression of genes related to cell migration and invasion of adjacent tissues. As a result, cancer cells are able to detach from the primary tumour, invade new tissues and spread to distant organs, making the disease more

difficult to treat.

The detection of TP53 mutations through genetic testing has become an essential tool in the approach to EC, allowing for personalised treatment. Understanding these mutations is essential for the search for targeted therapies, including MDM2 inhibitors, which block proteins responsible for p53 degradation, and gene therapies, which aim to restore the function of mutated TP53.

Thus, the TP53 mutation directly contributes to tumour progression, making EC more aggressive and resistant to conventional therapies. With advances in research, new therapeutic strategies are being developed to address this challenge, seeking ways to restore p53 function or explore alternative molecular pathways to contain tumour progression. The TP53 gene mutation has a significant impact on the prognosis of EC, directly influencing tumour aggressiveness, response to treatment, and patient survival rates. TP53 encodes the p53 protein, one of the body's main tumour suppressors, responsible for regulating the cell cycle and inducing apoptosis in cells with irreparable DNA damage. When this gene undergoes mutations, its protective function is compromised, allowing altered cells to proliferate uncontrollably, favouring tumour progression. Studies indicate that patients with TP53 mutations have reduced survival rates, especially those diagnosed with endometrial serous carcinoma, a highly aggressive subtype of the disease. The presence of this mutation is associated with accelerated tumour growth, increased risk of metastasis, and resistance to conventional treatments, making the prognosis more unfavourable.

The ability of tumour cells to activate apoptosis mechanisms is also compromised, hindering the efficacy of CT and RT. As a result, patients

with this mutation often present resistance to conventional treatments, requiring alternative therapeutic approaches, such as immunotherapy and targeted therapies. Given the negative impact of TP53 mutation on the prognosis of EC, new therapeutic strategies should be explored to improve clinical outcomes for patients..

Conclusion

Mutations in the TP53 gene play a crucial role in the development and progression of EC, especially in the most aggressive forms of the disease, such as serous carcinoma. The loss of p53 protein function, caused by mutations in TP53, compromises essential cellular control mechanisms, allowing uncontrolled proliferation of altered cells and favouring genomic instability. As a result, tumours with this mutation present accelerated growth, a higher risk of metastasis and resistance to conventional treatments, making the prognosis of patients more challenging. Identifying these mutations through genetic testing has proven to be a valuable tool for personalising treatment, allowing for more effective and targeted therapeutic approaches.

In addition, new strategies are being investigated to restore the function of mutated p53, including MDM2 inhibitors, which block proteins responsible for p53 degradation, and gene therapies, which seek to directly correct mutations in TP53.

With advances in research, it is expected that these new approaches may improve patient prognosis and offer safer and more efficient alternatives for the management of EC.

Understanding the molecular mechanisms involved in the TP53 mutation is essential for the development of innovative therapies that can positively impact patients' survival and quality of life.

Abbreviations

EC - Endometrial Cancer, CNV - Copy Number Mutation, DSBs - Double Strand Breaks, IHC - Immunohistochemistry, INCA - National Cancer Institute, IR - Ionizing Radiation, MSI - Microsatellite Instability, NGS - Next Generation Sequencing, qPCR - Real Time PCR, CT - Chemotherapy, RT - Radiotherapy, TCGA - Cancer Genome Atlas.

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