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The Regulatory Mechanism of Trp53R172H Mutation in the Metastasis of Pancreatic Ductal Adenocarcinoma Cells

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Abstract. Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal cancers. It is often diagnosed at a late stage, and is likely to spread, and has a 5-year survival rate of less than 7%. When it spreads, the prognosis deteriorates significantly. Fewer than 20% of patients are eligible for complete surgical resection. However, the reasons for its spread at the molecular level remain unknown. TP53 is the second most frequently mutated gene in PDAC, with alterations present in approximately 70% of cases, second only to KRAS. The Trp53R172H mutation, which is equivalent to human TP53R175H, is an important-gain-of-function-mutation. It cooperates with KrasG12D to promote PDAC progression and spread. This study aimed investigate out how Trp53R172H regulates the spread of PDAC cells and to define the underlying cellular and molecular mechanisms. To address these objectives, the study employed a systematically review of previous studies including in vitro cellular assays (including the establishment of gene-edited cell lines and Transwell assays for evaluating migratory and invasive capacities), in vivo animal models (via tumor xenotransplantation in nude mice), and molecular biology techniques (such as multi-omics analysis for screening differential molecules and chromatin immunoprecipitation (ChIP) for validating target gene binding). This study fills important gaps in the understanding of mutant p53 biology. It also provides new possible targets for clinical treatment of metastasis, and useful biomarkers that may enable early detection of metastatic risk.

Keywords: Trp53R172H, PDAC, Metastasis, Molecular mechanisms, Targeted therapy

1. Introduction

PDAC, which is the main type of pancreatic cancer, makes up 90% of all pancreatic cancers. It is hard to detect at an early stage and is likely spread a lot, so its 5-year survival is less than 7%, and people call it “the king of cancers” [1]. In 2020, global data showed more than 490 ,000 new PDAC cases and almost 460,000 deaths in the world, with 120,000 new cases in China. About half of patients are found to have spread far away, so the rate of radical resection is less than 20% [2]. PDAC metastasis includes steps like epithelial-mesenchymal transition (EMT) and breaking down the matrix outside cells, but the real molecular reasons are not clear, so there are no good targeted drugs [3].

In the genetic changes that push PDAC forward, the tumor suppressor gene TP53 has the most mutations in human cancers, with 70% of PDAC cases having this mutation, which is only less than

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KRAS (>90%) [1]. Trp53R172H (same as human R175H) is a common mutation in the DNA-binding part that has gain-of-function (GOF) features. It can work with KrasG12D to make PDAC spread and move to other parts, and this pro-metastatic effect was seen in KPwm/+C mouse models [4]. However, the exact mechanisms (like PI3K/Akt or Wnt dependence) and the target molecules through which this mutation controls metastasis are still not known [5].

The study wants to look at the connection between Trp53R172H and PDAC clinicopathological parameters and prognosis, check its effect on PDAC cell migration, invasion, and EMT, find important downstream pathways and target molecules, and see if targeting this pathway can help treat the disease. This work will not only fill the gap in how Trp53R172H helps metastasis and makes the understanding of mutant p53 biology richer, but also give clinically useful, biomarkers for early warning of metastasis and build a base for making targeted drugs [2,5].

The research brings together clinical analysis, in vitro tests, in vivo checks, and mechanism and therapy verification. In a clinical sample study, they found Trp53R172H by sequencing and linked it with clinical numbers and survival outlook. In vitro experiments, they made gene-edited cell lines and checked metastatic behavior with Transwell tests. For in vivo verification, they set up nude mouse transplant models, counted metastatic spots, and confirmed molecule expression. Also, through omics they picked out different molecules, used ChIP to find pathways, and tested how well inhibitors worked in mechanism and therapy verification [1,4].

2. The molecular ways of the Trp53R172H mutation

2.1. Impact on the cell cycle and programmed cell death

The Trp53R172H change (same as human TP53R175H) is a hot spot missense change in the DNA-binding part of the p53 tumor suppressor, and it profoundly disrupts normal cell cycle control and cell death signals. Unlike wild-type p53 that makes cell cycle stop by turning on target genes like p21 when cells get stressed, Trp53R172H shows a gain-of-function (GOF) behavior that promotes aberrant cell proliferation. Research on oral cancer models shows that Trp53R172H specifically increases Cyclin B1 by directly turning on its promoter. Cyclin B1 binds to cyclin-dependent kinase 1 (Cdk1) to form the maturation-promoting factor (MPF), which phosphorylates key substrates such as histone H1 and lamin proteins, triggering chromosome condensation and nuclear envelope breakdown to drive the G2/M phase transition. As a result, it accelerates the G2/M phase transition and promotes uncontrolled tumor growth [6]. Other models also support this pattern; this cancer-causing action is also backed by triple-negative breast cancer (TNBC) mouse models, where taking away Trp53R172H really slows down tumor moving forward and makes living longer, proving the change's important job in keeping tumor cell growth going [7].

In the area of apoptosis regulation, Trp53R172H stops the pro-apoptotic job of wild-type p53 by both dominant-negative effects and new activities. Studies on hematopoietic stress responses show that cells with Trp53R172H have less sensitivity to chemotherapy-induced apoptosis compared with p53-null cells, because the mutant protein impairs the initiation of apoptotic signaling cascades [8]. Importantly, the stabilization of the Trp53R172H protein is very important for its anti-apoptotic effects-drugs such as GY1-22 that reduce mutant p53 protein levels restore p21 expression and reactivate apoptotic pathways. This demonstrates the functional link between mutant p53 stability and apoptotic resistance [9]. In pancreatic cancer, Trp53R172H-driven neutrophil recruitment creates an immunosuppressive microenvironment that further suppresses apoptosis, which helps tumor cell survival even when there is therapeutic pressure [10].

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2.2. Chromosome stability and genome integrity

Trp53R172H is important in promoting chromosomal instability and undermining overall genome integrity, which is a big sign of cancer progression. Research on cell lines from oral tumors shows that when Trp53R172H is expressed, it is associated with centrosomes amplification and aneuploidy happening, which are major drivers of genomic instability [6]. This is not just due to loss of normal p53 job function but rather reflects a gain-of-function effect, as tumors with Trp53R172H exhibit more serious genome problems compared with tumors lacking p53. In acute myeloid leukemia with complex karyotype (CK-AML), Trp53R172H accelerates disease onset by promoting aberrant self-renewal in hematopoietic stem and progenitor cells (HSPCs) prior to fully change, and FOxh1 has been identified as a key mediator of this genome instability [11].

The mutant p53 protein disrupts DNA damage repair by interfering with the transcription activation of DNA repair genes. Unlike the normal p53, which helps fix DNA by activating pathways such as nucleotide excision repair, Trp53R172H impairs these processes by sequestering co-factors required for DNA- repair complex assembly. In competition bone marrow transplant tests, N-ethyl-N-nitrosourea-based experiments have demonstrated that mutant-p53 (Trp53R172H) drives clonal expansion of DNA-damaged HSPCs; notably, cells harboring Trp53R172H exhibit increased DNA damage following exposure to ENU, which elevates mutational burden and thereby facilitates this mutant-p53-driven clonal outgrowth of damaged HSPCs [11]. This genomic instability not only facilitates tumor initiation but also contributes to therapeutic resistance because it creates different kinds of tumor cells with diverse genetic changes.

2.3. Control of metastasis-related signaling pathways

The Trp53R172H mutation is a major driver of cancer spread, because it dysregulates multiple cellular signals. In esophageal squamous cell cancer (ESCC), this mutation establishes a new BRD4-CSF-1 path that helps lung metastasis. Trp53R172H binds to the CSF-1 promoter, and more H3K27ac at that spot helps BRD4 come, which leads to increased CSF-1 expression [12]. After that, the CSF-1/CSF-1R signal turns on STAT3 phosphorylation and causes EMT, which are very important for cancer to move and spread, enables cancer cells to lose epithelial characteristics (e.g., E-cadherin expression) and acquire mesenchymal traits (e.g., vimentin upregulation), thereby enhancing their motility, invasiveness, and ability to penetrate surrounding tissues and blood vessels. Inhibition of BRD4 in tumors with Trp53R172H lowers CSF-1 in the blood and stops lung metastasis, showing this path is a good target for treatment [12].

In squamous cell cancers, the Trp53R172H change gives pro-metastatic features by changing how cells move and invade. Recent research shows that this mutation induces increased expression matrix metalloproteinases (MMPs) and chemokine receptors get made, thereby enabling tumor cells to invade the extracellular matrix and colonize distant organs [13]. In pancreatic cancer models, Trp53R172H induces CXCL2 secretion, which recruits CD11b+Ly6G+ neutrophils to the tumor area. These neutrophils not only stop anti-tumor immunity but also promote blood vessel changes and metastatic niche formation [10]. Also, Trp53R172H works with oncogenic KrasG12D to make metastasis more likely. This is seen in KrasG12D/+, Trp53R172H/+ mice, which increases distant metastases than single-mutant mice [13].

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3. Clinical implications

3.1. Trp53R172H mutation change detection

Finding Trp53R172H correctly is very important for knowing the risk and giving personal treatment to cancer patients. Because it is found a lot in many cancers, like 60-70% of squamous cell cancers, 84% of TNBC, approximately 40-50% of CK-AML (core-binding factor acute myeloid leukemia), this mutation is a good marker for finding and predicting the disease [7,13]. Currently, people use some different ways to find the mutation, and next-generation sequencing (NGS) is seen as the best way. Special NGS tests can find Trp53R172H in FFPE tumor samples, ctDNA, and liquid biopsies, which allows non-invasive monitoring of disease dynamics [12].

For clinical samples with not much tumor content, droplet digital PCR (ddPCR) gives better sensitivity to find Trp53R172H. This way has been effectively used to find very small leftover disease (MRD) in AML patients after chemotherapy, because Trp53R172H-positive ctDNA amounts go together with the risk of relapse-this is due to the fact that ctDNA levels directly mirror the clonal dynamics of Trp53R172H-mutant cancer cells: rising ctDNA indicates expansion of therapy-resistant mutant clones that evade treatment pressure, while declining levels reflect effective elimination of these clones by therapy, thus enabling real-time assessment of treatment response and relapse risk [11]. Immunohistochemical (IHC) staining for mutant p53 protein is another method people use a lot, since Trp53R172H is more stable than the normal p53, which makes strong staining in the cytoplasm and nucleus [9]. But IHC needs to be checked by other molecular ways because it can react with other p53 mutants too. New improvements in digital pathology have made it better to measure how much mutant p53 is there, making IHC more useful for telling the future of TNBC and ESCC patients [7,12].

The Trp53R172H test is not only for finding cancer but also for telling how the disease will develop. In CK-AML, having the Trp53R172H change means people live shorter lives and the cancer comes back more often than if they have no p53 or normal p53. This makes it a big thing to think about when choosing treatment [11]. In the same way, ESCC patients whose tumors have Trp53R172H do not live as long because the cancer spreads more easily, which shows this change can tell us about the future [12]. Also, checking Trp53R172H amounts in ctDNA over time can guess if treatment is working. If the amount of the changed gene goes down after therapy, the patient usually gets better, but if the amount goes up, it means the treatment is not working and disease recurrence is likely [7].

3.2. Therapy and intervention strategies

The special GOF features of Trp53R172H have made people create new targeted treatments that address previously unmet therapeutic needs. One good idea is to get rid of mutant p53 protein so that wild-type p53 can work again. The small molecule GY1-22 was found to reduce the levels of Trp53R172H by promoting its degradation, thereby reactivating p21 expression; when combined with atorvastatin-which inhibits the dominant-negative (DN) activity of Trp53R172H (preventing the mutant protein from sequestering wild-type p53 and blocking its tumor-suppressive functions) - the combination exerts a synergistic anti-tumor effect, it makes mutant p53 break down more by stopping its dominant-negative effects [9]. This method has worked in animal tests, causing tumors regression and extending survival in animal models live longer, and now it is being tested in early human trials for serious solid tumors [9].

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Targeting downstream signaling pathways of Trp53R172H has also given good results. In ESCC, using JQ1 to stop BRD4 breaks the BRD4-CSF-1 axis, this makes CSF-1 less and stops lung metastasis [12]. Clinical trials are looking at using BRD4 inhibitors together with chemotherapy in patients with Trp53R172H-positive ESCC, early data shows they live longer without the disease getting worse [12]. For blood cancers, going after FOxh1-which is very important for how Trp53R172H causes leukemia-could stop leukemic stem cells from renewing themselves too much, like when FOxh1 was made lower in CK-AML mouse models and the disease started less [11].

Immunotherapy methods are also being made to fit Trp53R172H-positive tumors. In pancreatic cancer, Trp53R172H causing neutrophil recruitment makes it resist CD40 combination immunotherapy, so, neutrophil removal or CXCL2 blocking can get back immune sensitivit7 [10]. Clinical tests are looking at using anti-CXCL2 antibodies together with immune checkpoint inhibitors in Trp53R172H-positive pancreatic cancer [10]. Also, mutant p53 coming from neoantigens are being aimed at with custom cancer vaccines, because Trp53R172H expression makes immunogenic peptides that can cause anti-tumor T cell reactions [7]. Mutant p53 is an ideal neoantigen due to its tumor-specificity (absent in normal tissues), high immunogenicity (the amino acid substitution generates novel peptide epitopes recognized by T cells), and frequent occurrence across cancer types-traits that minimize off-target effects and maximize vaccine efficacy. Early preclinical research has shown that vaccination for Trp53R172H neoantigens lowers tumor growth and makes survival better in TNBC models [7].

Combination treatments that deal with several parts of Trp53R172H-driven cancer growth are emerging as promising strategies. For example, mixing mutant p53 breaking drugs with BRD4 blockers works together to stop tumor growth better, because they hit both the bad protein and the signals it starts [9,12]. In CK-AML, using FOxh1 blockers together with hypomethylating drugs has shown better results than using just one medicine, since it aims at both the leukemia stem cells making more of themselves and the DNA becoming unstable [11]. Also, sorting patients by if they have Trp53R172H is very important for getting the best treatment results-new patient information shows that Trp53R172H-positive TNBC patients get better from PARP blockers compared to patients with normal p53, because their DNA is more unstable and there is synthetic lethality [7].

4. Future directions

Even though major progress has been made in understanding how the Trp53R172H mutation contributes to PDAC metastasis, many important questions and knowledge gaps-unknown areas that span molecular mechanisms, tissue-specificity, and translational applications-still exist in the exploration of Trp53R172H-driven downstream genes and pathways, providing chances for future study. Despite notable progress in identifying key effectors (e.g., chemokine family members, SAA1/2, Foxh1) and perturbed signaling cascades (e.g., NF-κB, PI3K/AKT/mTOR), these findings remain fragmented, context-dependent, and far from comprehensive. Critical unknowns persist across multiple layers, which not only hinder a full understanding of Trp53R172H oncogenicity but also impede the development of targeted therapeutic strategies for cancers harboring this hotspot mutation. First, the manner in which Trp53R172H potentiates the oncogenic effects of other key genetic alterations in PDAC, such as KrasG12D, requires deeper investigation. While past research has demonstrated that KrasG12D acts as the primary driver oncogene and that Trp53R172H serves to augment KrasG12D-induced phenotypes including chromosome instability and metastasis, the precise molecular crosstalk at the genetic and post-transcriptional levels-including the involvement of non-coding RNAs, epigenetic regulators, and protein phosphorylation cascades- remains incompletely understood. Exploring how the Trp53R172H mutant remodels the KRAS-driven

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transcriptional network beyond its established interaction with FOXA1 could uncover novel regulatory nodes to target and constrain cancer metastasis in future translational studies. For example, integrating single-cell RNA sequencing and chromatin immunoprecipitation sequencing (ChIP-seq) methods could show cell-type-specific regulatory mechanisms in both cancer cells and the TME, as was used recently to look at heterogeneity in PDAC spreading [14].

Second, the different functions of Trp53R172H in various PDAC molecular subtypes need more study. Clinical research shows PDAC has different molecular subtypes with different patient outcomes and treatment responses, but how Trp53R172H affects metastasis in each type is not clear. Future studies should group PDAC patients by molecular type and correlate Trp53R172H mutation status with clinical features, like where the cancer spreads to (for example, liver or peritoneal metastasis) and treatment resistance. Also, examining whether Trp53R172H interacts with other cancer-causing genes in different subtypes to change how it spreads could give ideas for personalized therapy. Using lab models made for specific PDAC types, together with patient-derived xenografts (PDXs), would help support these studies focused on subtypes [15].

Third, the role of Trp53R172H in remodeling the TME and how it affects metastatic spread requires further study. New findings show that mutant p53 can alter communication between tumor cells and stromal components, like cancer-associated fibroblasts (CAFs), immune cells, and endothelial cells, to make a pro-metastatic microenvironment. But, the exact ways Trp53R172H controls the release of cytokines, chemokines, and extracellular matrix (ECM) components, and how these factors change immune cell infiltration and angiogenesis, are not completely clear. Later studies using spatially resolved transcriptomics and multiplex immunofluorescence could map the TME picture in Trp53R172H-mutant PDAC, finding important stromal targets that work with the mutation to promote metastasis [10]. Furthermore, given that Trp53R172H mutant remodels intercellular communication networks-by modulating cytokine secretion, immune cell infiltration, and stromal cell activation in the tumor microenvironment-exploring the combination of Trp53R172H-targeted therapies with immunotherapies or anti-stromal agents could identify novel synergistic treatment strategies [10].

Fourth, the development of more exact and clinically useful ways to target Trp53R172H is still a big problem. Now studies find FOXA1 is important for Trp53R172H promoting cancer spread, but it is hard to aim at the mutant p53 itself because its conformation is unstable. Later work should try to make small pills that can stick to the Trp53R172H mutant shape, to make it work like normal p53 or to break it down [16]. Also, using synthetic lethal ideas-where if another gene is lost, it only kills the Trp53R172H mutant cells-could give other ways to treat. High-throughput CRISPR-Cas9 screens and drug repurposing may help find these synthetic lethal partners and possible medicines faster, like one new study that found BRCA2 as a synthetic lethal target in Trp53R172H mutant PDAC [16].

Lastly, translational research that connects preclinical models and clinical practice is very important to move forward the clinical use of Trp53R172H-related discoveries. Future clinical trials looking at the prognostic and predictive value of detecting Trp53R172H mutation in PDAC patients are necessary to confirm its utility as a biomarker. developing non-invasive diagnostic tools-such as liquid biopsy assays designed to detect Trp53R172H-mutated circulating tumor DNA (ctDNA)-could facilitate treatment response assessment in PDAC, even though the clinical utility of such assays for early metastasis monitoring remains limited by the low ctDNA shedding rate inherent to PDAC, a consequence of its poor vascularization [17]. Long-term studies following Trp53R172H mutation changes during disease progression and treatment could further improve personalized intervention strategies, making sure that therapies are given at the best time of disease [17].

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To sum up, future research on Trp53R172H mutation in PDAC metastasis should use multi-omics technologies, advanced preclinical models, and clinical translational studies to address remaining mechanistic gaps and make effective therapeutic strategies. By clarifying out the complex networks controlled by Trp53R172H, improvement of the prognosis of PDAC patients with this aggressive mutation can be provided.

5. Conclusion

This research systematically examines the multiple mechanisms by which the Trp53R172H mutation helps PDAC progression and metastasis, aiming to fill critical gaps in the understanding of how mutant p53 causes cancer. The main results show that Trp53R172H has gain-of-function effects in several ways: it accelerates the G2/M phase progression to help cells grow without control; it inhibits cell death to make treatments less effective, it causes chromosomal instability to increase genetic differences; and it changes signaling pathways (like BRD4-CSF-1, CXCL2-neutrophil recruitment) to help metastasis and create an immunosuppressive tumor environment. In the clinic, Trp53R172H is seen as a useful biomarker for predicting how the disease will go and how patients will respond, with non-invasive detection methods like liquid biopsy allowing doctors to monitor the disease and treatment effects in real time. Treatments that target the mutation, such as drugs that degrade mutant p53, inhibitors of downstream pathways, and combination immunotherapies, show promising results in early studies, giving new chances for personalized care. Even with this progress, future work should focus on Trp53R172H's interaction with key drivers like KrasG12D, its subtype-specific roles in PDAC, its function in tumor microenvironment remodeling, and the development of precise targeted drugs. These are critical for dissecting core oncogenic and drug-resistant pathways, addressing PDAC heterogeneity to avoid one-size-fits-all treatments, overcoming immunotherapy resistance of "cold tumors", and filling the gap in PDAC precision therapy. Studies that connect lab findings to real patient care are very important to validate if the biomarkers work and to make treatments better. In the end, figuring out the complicated networks controlled by Trp53R172H gives a lot of hope for improving the prognosis for patients with this aggressive type of PDAC.

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