ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

Aberrant Signal Transduction Pathways in Pancreatic Ductal Adenocarcinoma: Current Perspectives on Molecular Targets

S. Kaviya[1]; G. SivaKumar[2]; P. Anandhasankar[3]

[1,2,3]Department of Pharmacology KMCH College of Pharmacy Coimbatore, India

Publication Date: 2026/08/20

Abstract: Pancreatic cancer is among the most aggressive neoplasms worldwide, with a significantly low five-year survival rate as reported in the literature. Pancreatic tumours are predominantly diagnosed as pancreatic ductal adenocarcinoma (PDAC), which is characterized by poor prognosis, late diagnosis, aggressive progression, and resistance to standard chemotherapy. Recent advances in the field of molecular and genomic biology have improved the understanding of the genetic underpinnings of this disease. The review discusses the key genetic drivers of pancreatic carcinogenesis, including KRAS, TP53, CDKN2A, SMAD4, and BRCA1/2. The mechanisms of action of these genes and their impact on the signaling pathways involved in the development and progression of PDAC are described. These genes encode proteins that participate in the regulation of the MAPK signaling pathway, cell cycle progression, TGF-β signaling pathway, and homologous recombination DNA repair mechanisms. The review emphasizes the role of these genes as therapeutic biomarkers for the development of targeted molecular therapy. The current management strategies targeting these mechanisms and the emerging therapeutic agents that may be considered in the future for the management of patients with pancreatic cancer are discussed.

Keywords: *Pancreatic Cancer, PDAC, KRAS, TP53, CDKN2A, SMAD4, BRCA, Targeted Therapy, Molecular Pathway.*

How to Cite: S. Kaviya; G. SivaKumar; P. Anandhasankar (2026) Aberrant Signal Transduction Pathways in Pancreatic Ductal Adenocarcinoma: Current Perspectives on Molecular Targets. *International Journal of Innovative Science and Research Technology*, 11(8), 1172-1189. https://doi.org/10.38124/ijisrt/26aug368

I. INTRODUCTION

Pancreatic cancer has continued to be one of the most aggressive and deadly forms of cancer in the world. It has become a major health challenge globally. Pancreatic ductal adenocarcinoma (PDAC) accounts for 90 to 95% of pancreatic cancers,[2] which are responsible for the majority of pancreatic-related deaths. Although there has been significant progress in the field of cancer research, including the development of new drugs to treat this deadly disease, the outlook for pancreatic cancer patients remains bleak, with only fewer than 10% surviving five years after diagnosis. According to recent global statistics, pancreatic cancer ranks among the top deadly cancers affecting the global health arena.[3]

Pancreatic ductal adenocarcinoma tends to grow without causing any significant clinical symptoms in the early stages, which often results in the silent spread of this deadly disease. In most cases, pancreatic cancer tends to spread to distant sites such as the liver, lungs, or peritoneum before diagnosis, which means only a small percentage of patients are likely to benefit from surgical intervention. In addition, recurrence often occurs after surgical intervention due to the aggressive nature of this tumor type.

On a molecular level, pancreatic cancer is characterized by a multitude of genetic and epigenetic alterations. Recent large-scale genomic analyses demonstrate that PDAC develops through the accumulation of mutations in a number of critical oncogenes and tumor suppressor genes involved in fundamental cellular processes such as cell proliferation, apoptosis, DNA repair, and cell-cycle progression. Among these alterations, mutations in the KRAS oncogene, TP53, CDKN2A, SMAD4, and BRCA1/2 are considered major alterations involved in pancreatic tumorigenesis.

The first genetic alteration involved in PDAC development involves the activation of the KRAS oncogene, which occurs in over 90% of pancreatic tumors. KRAS[6] mutations result in the persistent activation of downstream pathways such as MAPK/ERK and PI3K/AKT, which are involved in uncontrolled cell growth, metabolic changes, and resistance to cell death. Considering its critical role in the development and progression of pancreatic cancer, KRAS has long been considered a key therapeutic target. However, it has traditionally been considered an “undruggable” target. However, recent breakthroughs in the field of targeted drug development have led to the development of KRAS inhibitors such as sotorasib and adagrasib.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

In pancreatic cancer, the activation of KRAS often comes hand-in-hand with the silent inactivation of several tumor-suppressing genes. TP53, for example, which has been mutated in 70-75% of pancreatic cancers, is a tumor suppressor that coordinates the integrity of the genome, including DNA repair, apoptosis, and the pause button for the cell cycle. When TP53 is mutated, the tumor-suppressing activity of this gene disappears, and it can sometimes assume tumor-promoting functions. Researchers are currently exploring ways to reactivate this tumor suppressor or to target the mutant p53 protein as a new avenue for therapy.

Another important tumor suppressor in pancreatic cancer is CDKN2A, which produces the tumor suppressor protein p16. It sits at the critical checkpoint between the G1 and S phases of the cell cycle. When this tumor suppressor is inactivated, the cell cycle goes haywire with uncontrolled activity of CDK4 and CDK6. Researchers are currently exploring this new avenue for therapy with drugs such as palbociclib and ribociclib.

Another tumor suppressor, SMAD4, is often affected in PDAC. This tumor suppressor is a part of the TGF-β pathway, which regulates cell differentiation, growth, and death. When the tumor suppressor SMAD4 is eliminated, the TGF-β pathway becomes dysfunctional, and the cancer progresses, metastasizes, and invades. There have been some positive results from clinical trials of inhibitors of the pathway, such as galunisertib. The role of defects in DNA repair, particularly mutations of the tumor suppressors BRCA1 and BRCA2, has also been acknowledged as a significant factor in the causation of pancreatic cancer. These genes play a crucial role in the process of DNA repair by the mechanism of homologous recombination. When these genes mutate, the cancer becomes more susceptible to the effects of PARP inhibitors. These inhibitors target cancer cells by synthetic lethality. There have been positive results from trials of PARP inhibitors, such as olaparib and veliparib, particularly for cancer cells carrying mutations of the BRCA genes. [23]

The new insights provided by genome sequencing and other techniques have shown that PDAC is a heterogeneous cancer, and there are many different types of cancer, each having its own genetic and pathway "quirks." This highlights the importance of precision medicine. A better understanding of the interactions between the key cancer pathways and the targets they offer is the key to the future.

In spite of a tremendous amount of research, current therapeutic options for the management of pancreatic cancer are limited. Patients with pancreatic cancer develop resistance to chemotherapy and other drugs. Therefore, there is an urgent need for new targets and new therapeutic options to manage this deadly disease. This review attempts to identify the major genetic events involved in the development of pancreatic ductal adenocarcinoma, with particular emphasis on KRAS, TP53, CDKN2A, SMAD4, and BRCA1/2. In addition, this review attempts to identify the current therapeutic options and new drugs that target these genes and their pathways. Such new therapeutic options may lead to a better outcome for patients with pancreatic cancer.

II. MOLECULAR PATHOGENESIS OF PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDAC) develops through a complex multi-step process with the gradual accumulation of genetic and epigenetic alterations. These alterations convert normal pancreatic ductal cells into cancer cells with uncontrolled growth and invasive properties. PDAC development involves a number of factors, which include oncogene activation, tumor suppressor gene inactivation, alterations in intracellular signaling, and interactions with the tumor microenvironment. PDAC tumors are known for their genetic heterogeneity. However, large-scale genomic analysis has revealed that a relatively small number of core signaling pathways are consistently affected during PDAC development.

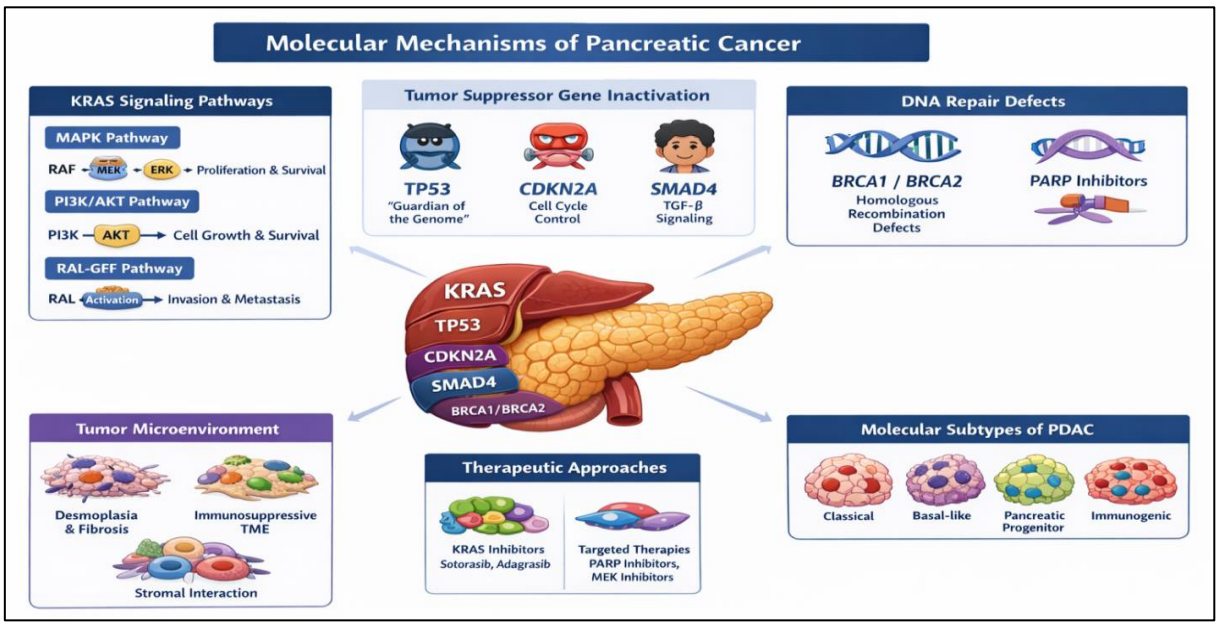

Fig 1 Molecular Mechanism of Pancreatic Cancer

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

➢ *Stepwise Genetic Progression of PDAC*

The genetic and molecular evolution of pancreatic cancer develops along a well-established pathway of progression from normal pancreatic ductal cells to invasive carcinoma through a series of precursor stages of cancer, termed pancreatic intraepithelial neoplasia (PanIN). PanINs are classified as PanIN-1 (low-grade), PanIN-2 (intermediate-grade), and PanIN-3 (high-grade) dysplasias. Each of these stages of PanINs is associated with particular genetic events, and these stages of progression from normal to tumor cells occur gradually. Thus, the progression of cancer from normal pancreatic ductal cells to invasive carcinoma occurs through a series of PanIN stages.

The initial genetic changes in the progression of PDAC involve the activation of the KRAS oncogene, and KRAS mutations occur in more than 90% of pancreatic cancer cases. KRAS mutations lead to the continuous activation of downstream targets of KRAS, which control cell proliferation, survival, and metabolism. Thus, the presence of KRAS mutations in the earliest stages of PanIN indicates the importance of these mutations as the initial genetic events in the progression of pancreatic cancer.

As these early lesions progress further into higher grades, they accumulate more genetic mistakes. Among the most common of these is the inactivation of the tumor suppressor gene CDKN2A, which codes for the p16 protein, which regulates the G1-S cell cycle checkpoint. The inactivation of p16 leads to unregulated cell division, thereby propelling the transition from precancerous changes to cancer. However, in the later stages of pancreatic cancer, there are mutations in other tumor suppressor genes, such as TP53 and SMAD4. The TP53 mutations impair genome stability and the ability of the cell to undergo programmed cell death, whereas the inactivation of the SMAD4 gene impairs the ability of the tumor to metastasize by affecting the TGF-β signaling pathway. These mutations are often associated with high-grade PanIN lesions and pancreatic cancer. The cumulative effect of the genetic mutations drives the normal pancreatic cell towards malignant transformation, characterized by unregulated cell growth, invasion, and metastasis.

➢ *The KRAS Signaling Role in Pancreatic Cancer*

Activating mutations of KRAS have come to be regarded as the key mechanism underlying the pathogenesis of pancreatic ductal adenocarcinoma. Among the genetic alterations associated with PDAC, mutations of KRAS are the most common, occurring in more than 90% of cases. These mutations occur at codons G12, G13, and Q61, keeping the KRAS protein locked in the active state. When KRAS is mutated, it becomes locked into the GTP-bound state, continuously activating downstream pathways controlling cell growth, differentiation, and survival. KRAS, being a GTP-binding protein, functions as a switch between the GDP-bound inactive form and the GTP-bound active form. This switch is regulated by signals from various growth factor receptors. However, cancer-causing mutations of KRAS render the KRAS protein unable to switch back to the inactive GDP-bound form, as a result of diminished GTPase activity. This results in the continuous activation of cell growth and survival pathways, thereby contributing to cancer. Several pathways are activated as a result of KRAS mutation, and the MAPK pathway, consisting of the RAF-MEK-ERK cascade, is the most studied. This pathway, when activated by KRAS, results in the transcription of genes involved in cell survival and proliferation, and its continuous activation is a key contributor to the uncontrolled cell division of cancer cells.

KRAS not only flips one switch; it fires up an entire network. One such pathway that KRAS heavily influences includes the PI3K/AKT pathway. This pathway regulates cell metabolism, survival, and the avoidance of apoptosis. When PI3K is activated, this results in the phosphorylation of AKT. This, in turn, results in cell survival by reducing pro-apoptotic signals and activating growth metabolism. When combined with the MAPK pathway, KRAS mutations result in a variety of cancer hallmarks, such as increased growth rate, resistance to apoptosis, and changes to metabolism.

Another pathway that KRAS influences includes the RAL-GEF pathway. This pathway regulates the movement, invasion, and metastasis of cancer cells. The combined effect of these pathways by KRAS mutations creates a fertile ground for cancer to flourish.

Due to its central role in pancreatic cancer, KRAS has long been considered a key therapeutic target. However, for a long time, direct targeting has been notoriously difficult. KRAS has thus been considered an “undruggable” target. However, this may not be true anymore with recent breakthroughs in drug discovery. Some innovative drugs targeting KRAS mutations, such as KRAS G12C, have been found to be effective in a variety of cancers. These include sotorasib and adagrasib, which trap mutant KRAS in its inactive state.

While KRAS G12C mutations are less prevalent in pancreatic cancer than in lung cancer, these advances have revived interest in the KRAS signaling pathways. Current research is also looking into the inhibition of downstream effectors such as MEK, ERK, and PI3K, as well as the application of combination therapy in overcoming drug resistance.[7]

In summary, the activation of KRAS is central in the development and progression of pancreatic cancer, as it regulates various signaling pathways that control cell growth, survival, metabolism, and spread. A better understanding of the KRAS signaling pathways and how they interact with other pathways could provide the key to the development of new and more effective treatments for pancreatic cancer.

➢ *Tumor Suppressor Gene Inactivation*

In addition to the activation of oncogenes, the inactivation of tumor suppressor genes plays a crucial role in the development of pancreatic ductal adenocarcinoma. Tumor suppressor genes regulate the normal progression of cell cycles, DNA repair, apoptosis, and genome stability. The inactivation of tumor suppressor genes, as a result of mutations, deletions, or epigenetic alterations, leads to the

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

loss of control in cell cycles, resulting in the development of pancreatic cancer.

The genes that are often mutated in pancreatic cancer include TP53, CDKN2A, and SMAD4. These genes are essentially the guardians of cellular balance, and when they are mutated, pancreatic cancer often develops and grows more quickly.

The TP53 gene, also called the "guardian of the genome," is mutated in 70-75% of pancreatic cancer cases. TP53 codes for the p53 protein, which is a transcription factor that monitors cellular stress and DNA damage. If DNA damage is detected, the cell stops and repairs the DNA, or in the worst-case scenario, the cell dies. A mutated TP53 gene, therefore, leads to the survival and proliferation of cancerous cells. In some cases, the mutated gene can even develop new powers that help the cancer progress.

The CDKN2A gene, also called cyclin-dependent kinase inhibitor 2A, is a tumor suppressor gene in pancreatic ductal adenocarcinoma. This gene codes for the p16INK4A protein, which regulates CDK4 and CDK6. These proteins, in turn, control the cell cycle by regulating the transition from the G1 phase to the S phase. A mutated CDKN2A gene, therefore, leads to the uncontrolled activation of CDK4 and CDK6, resulting in the rapid progression of cancer.[18]

Another tumor suppressor, SMAD4, is often silenced in pancreatic cancer. This tumor suppressor acts as a mediator of the transforming growth factor beta (TGF-β) pathway. This pathway plays a role in differentiation, cell growth, and apoptosis. When the tumor suppressor SMAD4 is absent, the tumor-suppressive effects of the TGF-β pathway are reduced, and the cancer progresses, becomes invasive, and metastasizes. Loss of the tumor suppressor SMAD4 expression often results in aggressive cancer and poor prognosis for patients with PDAC.

The silencing of these tumor suppressor genes alters the cell's signal transduction pathways, increasing cell growth, inhibiting apoptosis, and enhancing metastatic capabilities. These genetic mutations occur in the late stages of the development of pancreatic cancer.

The knowledge of the molecular events occurring when these tumor suppressors fail to perform their roles provides a therapeutic target for the treatment of pancreatic cancer. Researchers have identified several targets to restore the tumor suppressor functions or target the pathways activated by the tumor suppressors, and these targets may lead to the improvement of the treatment of pancreatic cancer.

- *DNA Damage Repair Defects*

Altered DNA damage repair processes also play a role in the progression of pancreatic cancer. This includes changes to the BRCA1 and BRCA2 genes, which affect the process of homologous recombination. This process, as discussed, is the precise mechanism of DNA double-strand break repair. When these genes are altered, the process of DNA repair becomes inaccurate, and mutations accumulate, driving cancer progression [23, 24].

Pancreatic cancer, as a result of alterations to the BRCA genes, becomes more susceptible to DNA-damaging agents. These cancer types have shown increased sensitivity to platinum-based therapies and PARP inhibitors, taking advantage of the synthetic lethality concept. PARP enzymes play a role in the repair of single-strand breaks. When these enzymes are inhibited, the breaks become double-strand breaks, which are lethal to cancer cells already compromised by BRCA mutations [23, 26].

The identification of BRCA mutations in a subset of pancreatic cancer patients has encouraged the use of targeted therapies. This includes the use of the PARP inhibitor, olaparib, which showed improved progression-free survival of patients with metastatic pancreatic cancer and BRCA mutations. This highlights the role of identifying DNA damage repair defects to guide the therapeutic approach for the treatment of pancreatic cancer.

- *Tumor Microenvironment and Stromal Interaction*

Apart from the genetic changes in tumor cells, the tumor microenvironment (TME) plays an important role in the development and progression of pancreatic ductal adenocarcinoma. PDAC is known for the presence of an extensive fibrotic stroma, also called desmoplasia. Desmoplasia consists of cancer-associated fibroblasts, pancreatic stellate cells, and the tumor microenvironment.

In the case of PDAC, the stromal fraction of the tumor can account for 80-90% of the tumor mass, forming physical and chemical barriers to the movement of therapeutics. The tumor microenvironment also plays an important role in tumor development by influencing signaling pathways that enhance tumor growth.

One of the hallmarks of the tumor microenvironment in PDAC is its immunosuppressive nature. The interaction between tumor cells, stromal cells, and the tumor microenvironment often acts in an immunosuppressive manner, thus evading detection by the immune system and reducing the effectiveness of immunotherapy.

The interaction between tumor and stromal cells activates pathways that are involved in tumor metastasis, angiogenesis, and inflammation. As the tumor microenvironment plays an important role in the development and progression of PDAC, research on the tumor microenvironment and stromal interaction is gaining momentum in the context of pancreatic cancer.

- *Molecular Subtypes of PDAC*

Recent advances in gene expression and transcriptomics have led to the discovery that pancreatic ductal adenocarcinoma (PDAC) is not an homogeneous disease, but that it consists of different molecular subtypes, each with its unique transcriptional signature and clinical outcome. The most commonly recognized subtypes of PDAC

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

include classical, basal-like/squamous, pancreatic progenitor, and immunogenic PDAC [28].

These subtypes vary in their biology, response to treatment, and clinical outcome. Classical PDAC, for example, is often associated with favorable outcome and response to certain treatments, while basal-like PDAC is more aggressive and is associated with poor outcome and reduced survival.

The molecular heterogeneity of PDAC is an important discovery that has significant clinical implications. The ability to identify unique gene expression signatures in each subtype of PDAC means that patients can be treated based on the molecular signature that their tumor expresses, making the discovery of PDAC subtypes an important driver of precision medicine.

III. KRAS SIGNALING PATHWAY AND TARGETED THERAPEUTIC STRATEGIES IN PANCREATIC CANCER

The Kirsten rat sarcoma viral oncogene homolog gene mutations are among the first and the most common mutations in PDAC. Approximately 90-95% of pancreatic cancer tissues have activating mutations in the KRAS gene, demonstrating the significance of this gene in the onset and progression of PDAC [6,34]. These mutations occur early in the process, in the development of pancreatic intraepithelial neoplasia, and are critical for the onset and growth of the cancerous cells [35]. Considering that KRAS controls various critical downstream targets, it has remained a primary gene for therapeutic intervention in pancreatic cancer.

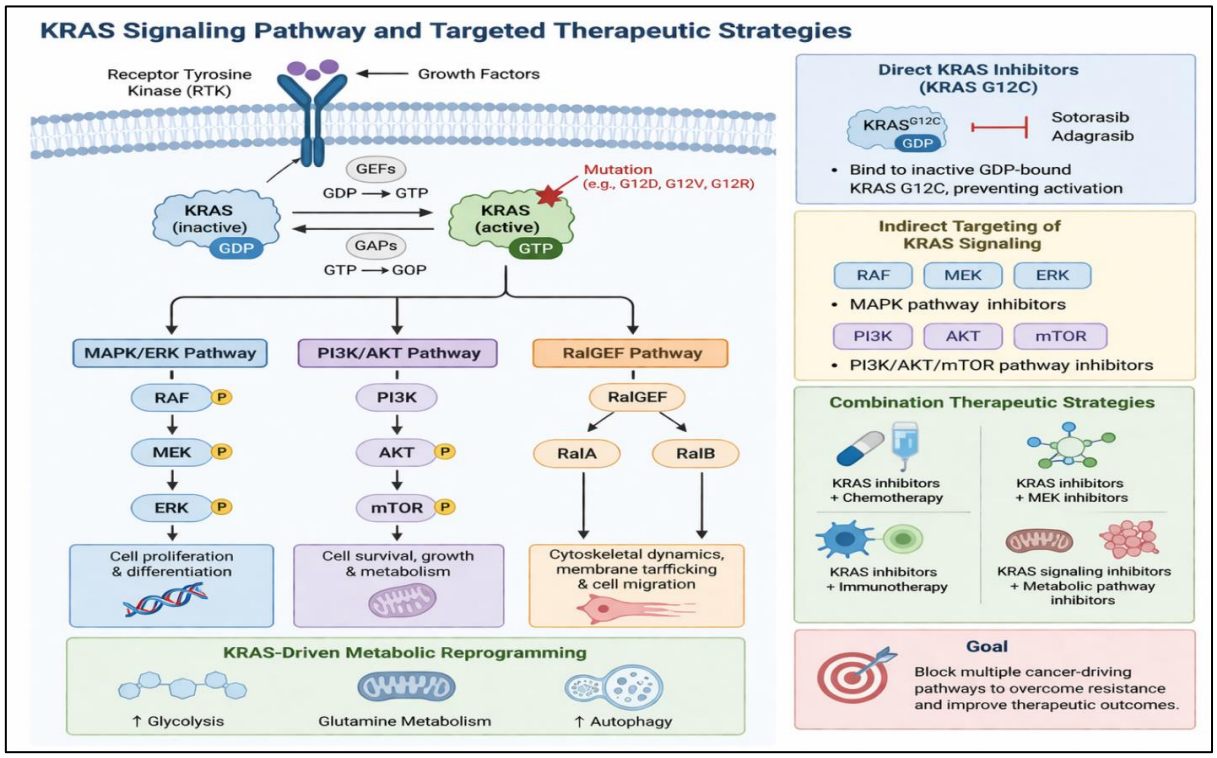

Fig 2 KRAS Signaling Pathway and Targeted Therapeutic Strategies

➢ *Structure and Function of KRAS*

KRAS is a part of the RAS gene family, a group of small GTP-binding proteins that function as a switch in the transmission of cellular signals from the cell membrane to the cell interior, affecting cell growth, survival, and differentiation [38]. Under normal conditions, the KRAS gene exists in an active state as a GDP-bound protein and in an inactive state as a GTP-bound protein.

The interconversion from an active state to an inactive state and vice versa is mediated by two types of proteins. Guanine nucleotide exchange factors (GEFs) are proteins that catalyze the exchange of GDP for GTP, activating the KRAS gene, whereas GTPase-activator proteins (GAPs) accelerate the hydrolysis of GTP to GDP, inactivating the KRAS gene.

As a result, the cancerous mutations disrupt the natural control mechanism by disabling the GTPase activity of KRAS. As a result, KRAS continuously signals for cell growth, even when there is no external stimulus for cell division [38]. Most of the KRAS mutations occurring in pancreatic cancer have the codon 12 mutation, where the G12D, G12V, and G12R mutations occur, thereby altering the shape of the KRAS molecule and enhancing its cancer-causing ability [6, 34].

➢ *Downstream Signaling Pathways Activated by KRAS*

Once KRAS is activated by the cancerous mutations, it activates various internal cell pathways, which, as a collective process, promote the development of cancer [34, 37]. These pathways include the MAPK/ERK pathway, the PI3K/AKT

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

pathway, and the RalGEF pathway, all of which influence different aspects of pancreatic cancer [38].

The MAPK pathway represents a significant pathway activated by KRAS. KRAS activation by cancerous mutations activates the RAF kinase, thereby activating the MAPK pathway. This activation of the MAPK pathway results in the activation of the ERK pathway, which, once activated, regulates the transcription factors controlling genes related to cell proliferation and differentiation [38]. Activation of the ERK pathway by the cancerous mutations of KRAS promotes the continuous cell division of the tumor, thereby enhancing the progression of the tumor.

The PI3K/AKT pathway is another important pathway that is initiated by KRAS. It plays a role in the regulation of metabolic functions, cell survival, and the prevention of cell death. When PI3K is activated, this leads to the phosphorylation of AKT, which then goes on to regulate many downstream molecules that play a role in the regulation of proteins, glucose metabolism, and the prevention of cell death. Through this pathway, KRAS is able to ensure the survival of the tumor cell.

KRAS is also able to initiate the RalGEF pathway. Together with RalA and RalB, this pathway is able to regulate the cell membrane, the cytoskeleton, and the migration of the cell. All these functions play a role in the metastasis of the cancer.

Thus, KRAS is able to initiate many important pathways that play a role in the growth and metastasis of the pancreatic cancer cell.

➢ *KRAS-Driven Metabolic Reprogramming*

KRAS is able to play a role in the growth of the pancreatic cancer cell. KRAS is able to alter the metabolic functions of the cell. The KRAS mutations activate the reprogramming of cellular metabolism, which increases the activity of glycolysis, glutamine metabolism, and autophagy. These changes provide the energy and the precursors required for the high growth rates of the tumor. They enable the pancreatic cancer cells to remain in the state of high metabolism even in the presence of stressful stimuli. KRAS mutations also regulate the amount of various metabolic enzymes and nutrient transporters, thus supporting the high octane state of metabolism. These changes are the hallmark of the aggressive nature of pancreatic ductal adenocarcinoma and offer new avenues of research that could be explored as therapy.

➢ *Historical Challenges in Targeting KRAS*

KRAS has been one of the most difficult targets in the history of cancer therapy. KRAS is difficult to target with small molecules due to the absence of binding sites in its structure. These difficulties have led researchers to describe KRAS as an “undruggable” target. The initial approaches tried to target the post-translational modifications that KRAS requires for its activity, particularly the farnesylation of KRAS. However, the clinical trials of farnesyl transferase inhibitors showed disappointing results as KRAS has alternative prenylation pathways that enable it to remain active.

Due to these hurdles, the focus has turned to downstream targets like MEK, PI3K, and ERK. Although the preclinical results are promising, the results in pancreatic cancer have been disappointing, mainly due to redundancy in the pathway.

➢ *Development of Direct KRAS Inhibitors*

Advances in structural biology and rational drug design have opened the door to direct inhibitors of KRAS, particularly for the KRAS G12C mutation. The mutation contains a reactive cysteine residue that can be targeted by covalent inhibitors.

Among the most active agents are sotorasib and adagrasib. These drugs specifically bind to the inactive GDP-bound state of the mutant KRAS G12C protein, preventing it from activating to the active state. Sotorasib has demonstrated significant efficacy as a KRAS inhibitor, with positive results in cancers with the KRAS G12C mutation. Adagrasib has also demonstrated promising antitumor activity against various KRAS mutant solid tumors. Although the frequency of the KRAS G12C mutation is lower in pancreatic cancer than in other cancers, this important step forward in direct KRAS inhibition has been significant.

➢ *Indirect Targeting of KRAS Signaling*

Since KRAS mutations in pancreatic cancer are still not directly targetable, alternative approaches are being taken to inactivate the KRAS signaling network. The most commonly used approach is to target the MAPK signaling network by targeting the RAF, MEK, and ERK kinases. For example, MEK inhibitors have been found to demonstrate their ability to slow tumor growth in preclinical studies of KRAS mutant pancreatic cancer. Another approach is to target the PI3K/AKT/mTOR signaling network, which is one of the key regulators of tumor cell survival and metabolism. It has been found that targeting both the MAPK and PI3K signaling pathways could be more effective in treating pancreatic cancer than targeting either pathway individually, thus avoiding the development of resistance, which is often seen upon targeting one particular pathway.

➢ *Combination Therapeutic Strategies*

Since KRAS mutant pancreatic cancer involves a complex network of signaling, alternative approaches are being taken to enhance the effectiveness of KRAS inhibitors in treating pancreatic cancer. Some of the current ideas being researched include:

- KRAS inhibitors in combination with chemotherapy
- KRAS inhibitors in combination with MEK inhibitors
- KRAS inhibitors in combination with immunotherapy
- Simultaneously targeting KRAS signaling and metabolic pathways

The goal is to inhibit several cancer-causing pathways at the same time, making it more difficult for cancer cells to

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

turn on alternative survival mechanisms and develop resistance to drugs.

➢ *TP53 Mutations and Targeted Therapeutic Strategies in Pancreatic Cancer*

TP53 is an undisputed cornerstone in cancer biology, and it encodes for the tumor suppressor protein p53, which is an essential transcription factor that maintains the integrity of the genome. The TP53 gene is located on chromosome 17p13.1, and it controls several cellular processes, such as cell cycle arrest, DNA repair, apoptosis, and senescence, in such a way that damaged cells are unable to progress in the cell cycle. It is in this regard that the tumor suppressor p53 is referred to as the "guardian of the genome."

TP53 mutations are present in 70-75% of pancreatic ductal adenocarcinoma (PDAC) cases, thus making it one of the most commonly mutated genes in pancreatic cancer.

- *Structure and Functional Domains of p53*

p53 consists of several distinct domains that are essential in its ability to regulate gene transcription and respond to cellular stress. The main domains include the N-terminal transactivation domain, the central DNA-binding domain, and the C-terminal oligomerization domain.

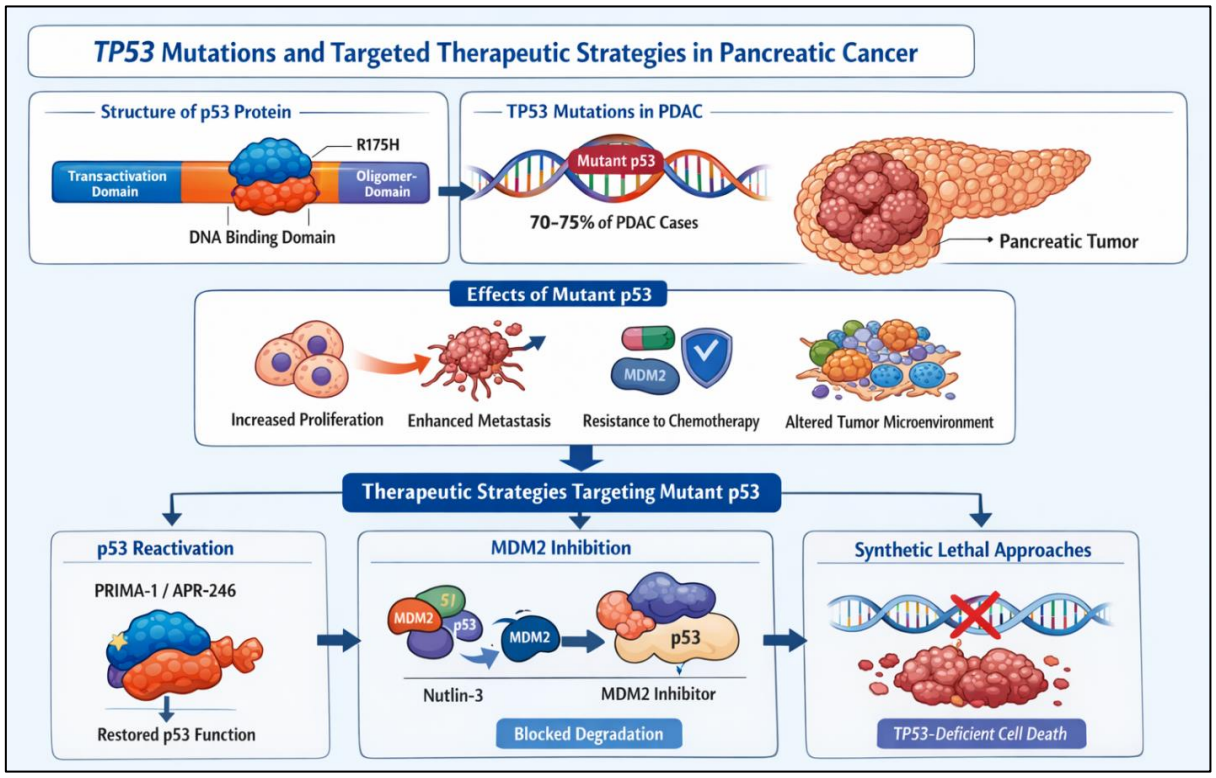

Fig 3 TP53 Mutations and Targeted Therapeutic Strategies in Pancreatic Cancer

- ✓ The transactivation domain interacts with the transcription machinery and other regulators, facilitating the ability of p53 to modulate genes that are involved in cell cycle and apoptosis.
- ✓ The DNA-binding domain binds to particular DNA sequences in the promoters of genes that are targets of the p53 tumor suppressor.
- ✓ The oligomerization domain enables the tetramerization of p53, a state that is required for transcription.

In normal cells, the level of p53 is maintained at a low level by the E3 ubiquitin ligase MDM2, which continuously targets p53 for degradation. However, in response to cellular stresses such as DNA damage, oxidative stress, oncogene activation, and low oxygen, the level of p53 increases in the nucleus. Consequently, p53 initiates transcriptional responses that arrest the proliferation of cells that have suffered DNA damage.

- *Physiological Functions of p53 in Cellular Homeostasis*

The antitumor capability of the tumor suppressor p53 is mediated by a variety of critical functions. One such function is the enforcement of cell cycle checkpoints, particularly at the transition from the G1 phase to the S phase. DNA damage triggers an increase in the expression of the cyclin-dependent kinase inhibitor, p21, also known as CDKN1A, by p53. This inhibitor prevents the activation of CDK2 and CDK4/6, resulting in the inability to phosphorylate the retinoblastoma protein.

If DNA damage is too extensive to repair, p53 initiates apoptosis, programmed cell death, by activating pro-apoptotic genes such as BAX, PUMA, and NOXA. In addition, p53 can induce senescence, a state in which the cell permanently stops dividing, preventing potentially cancerous cells from propagating.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

In addition to these functions, p53 regulates genes involved in DNA repair, oxidative stress response, and cellular metabolism. It is the central regulator in preventing oncogenic transformation.[12]

- *TP53 Mutations in Pancreatic Ductal Adenocarcinoma*

TP53 mutations are a significant genetic alteration in the development of pancreatic cancer. TP53 mutations differ from KRAS mutations in that TP53 mutations occur at a later stage in cancer development, specifically in the transition from high-grade PanIN lesions to invasive cancer.

TP53 mutations in pancreatic cancer consist mainly of missense mutations in the DNA-binding region of the TP53 protein. These mutations affect the ability of the TP53 protein to regulate its target genes.

The consequences of TP53 mutations may be categorized into two types. Firstly, the tumor-suppressive activity is compromised, which prevents cell-cycle arrest, DNA repair, or apoptosis. Secondly, the mutant p53 proteins may acquire novel functions that facilitate tumor progression.

The gain of novel functions of the mutant p53 proteins includes:

- ✓ Increased cell proliferation
- ✓ Increased metastatic capability
- ✓ Resistance to chemotherapy
- ✓ Alteration of the tumor microenvironment

Mutant p53 proteins may interact with other transcription factors that alter the gene expression patterns, which may facilitate the development of tumors. In pancreatic cancer, TP53 mutations often coexist with KRAS, CDKN2A, and SMAD4 mutations, which may form a complex network that facilitates the progression of cancer.

- *Role of TP53 Mutations in Tumor Progression and Metastasis*

TP53 mutations significantly affect the progression and metastasis of pancreatic cancer. The loss of p53 checkpoint mechanisms allows the accumulation of genetic changes, which may lead to genomic instability.

Genomic instability is one of the major reasons for tumor heterogeneity, which plays a significant role in the progression of pancreatic cancer.

Mutant p53 proteins are also known to induce epithelial-mesenchymal transition (EMT) in epithelial cells. EMT results in epithelial cells losing their characteristics and gaining the characteristics of mesenchymal cells. This results in cancer cells detaching from the main tumor site, invading other tissues, and forming metastatic sites. The metastatic sites are usually located far from the main tumor site, such as the liver or lungs. Therefore, the aggressive nature of pancreatic cancer and its usually poor outcome can be explained by the aforementioned characteristics.[40]

- *Therapies Targeting Mutant p53*

Since TP53 mutations are a major characteristic of pancreatic cancer, mutant p53 has become a major area of research. One such therapy involves the reactivation of mutant p53 by the use of small molecules that can induce the reversion of mutant p53 to its normal shape. Such a molecule has been identified to be PRIMA-1 (p53 reactivation and induction of massive apoptosis). APR-246 (Eprenetapopt) is a derivative of PRIMA-1. This molecule has been known to bind with mutant p53, thus reactivating it to its normal shape. The reactivated mutant p53 can induce the expression of pro-apoptotic genes.

Another strategy targets the interaction between MDM2 and p53. In cancer cells, the p53 tumor suppressor pathway may be suppressed by overexpression of MDM2, which causes p53 to be degraded. This overexpression of MDM2 results in the suppression of the tumor suppressor function of p53. Small molecules, such as Nutlin-3, have been shown to interfere with the interaction between MDM2 and p53, thus restoring the tumor suppressor function of p53.[13]

Other strategies target synthetic lethal interactions of TP53-deficient cancer cells. These synthetic lethal interactions target alternative DNA repair pathways, which are crucial for the survival of TP53-deficient cancer cells. These alternative DNA repair pathways could lead to the killing of cancer cells lacking TP53.[28]

- *Combination Therapies Involving p53 Pathway Modulation*

The p53 pathway regulates many other pathways, and as a result, various combination therapies have been developed to improve the effectiveness of cancer treatment. Combination therapies, for instance, could combine p53-reactivating agents and other cancer therapies. Combination of p53-reactivating agents and chemotherapy or other cancer therapies could improve the killing of cancer cells. Combination of p53-reactivating agents and chemotherapy could improve the killing of cancer cells by re-sensitizing cancer cells to DNA damage.

In a similar vein, targeting mutant p53 along with other cancer-causing pathways, such as KRAS or cell-cycle pathways, may enhance anti-cancer activity by a synergistic effect. This model has particular relevance to pancreatic cancer, which involves a complex network of genetic alterations to sustain cancer progression.

➢ *Cdkn2a and Cell Cycle Dysregulation in Pancreatic Ductal Adenocarcinoma*

CDKN2A is one of the frequently disabled tumor suppressors in PDAC and is located on chromosome 9p21. CDKN2A encodes two distinct tumor suppressor proteins that play significant roles in the prevention of pancreatic ductal adenocarcinoma. These two tumor suppressor proteins, p16INK4A and p14ARF, are part of two major tumor suppressor pathways: the RB pathway and the p53 pathway. These two pathways play important roles in the regulation of cell cycles.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

Approximately 80-95% of pancreatic ductal adenocarcinoma cases involve the loss of CDKN2A. Thus, the loss of CDKN2A is the most common alteration observed in pancreatic ductal adenocarcinoma. When the CDKN2A tumor suppressor is disabled, the cell cycle is significantly compromised. Thus, the cell cycle plays a pivotal role in the pathogenesis and progression of pancreatic ductal adenocarcinoma.

- *Structure and Genetic Organization of CDKN2A*

The CDKN2A gene is unique in that it encodes two separate tumor suppressor proteins from the same gene region, using alternative first exons and reading frames. These proteins are:

✓ p16INK4A (p16) – a cyclin-dependent kinase inhibitor that modulates the RB pathway

✓ p14ARF – a tumor suppressor that modulates the p53 pathway

Even though these proteins are products of the CDKN2A gene, they function independently and have separate tumor suppressor mechanisms.

The function of p16INK4A is to inhibit the function of cyclin-dependent kinases CDK4 and CDK6, which normally phosphorylate the retinoblastoma (RB) tumor suppressor. When RB is in the hypophosphorylated state, it binds E2F transcription factors, preventing the transcription of genes that are necessary for DNA synthesis. This prevents the cell from moving from the G1 phase into the S phase.

The function of p14ARF, on the other hand, is related to the tumor suppressor function of the p53 gene. P14ARF prevents the degradation of the tumor suppressor p53 by inhibiting the E3 ubiquitin ligase MDM2.

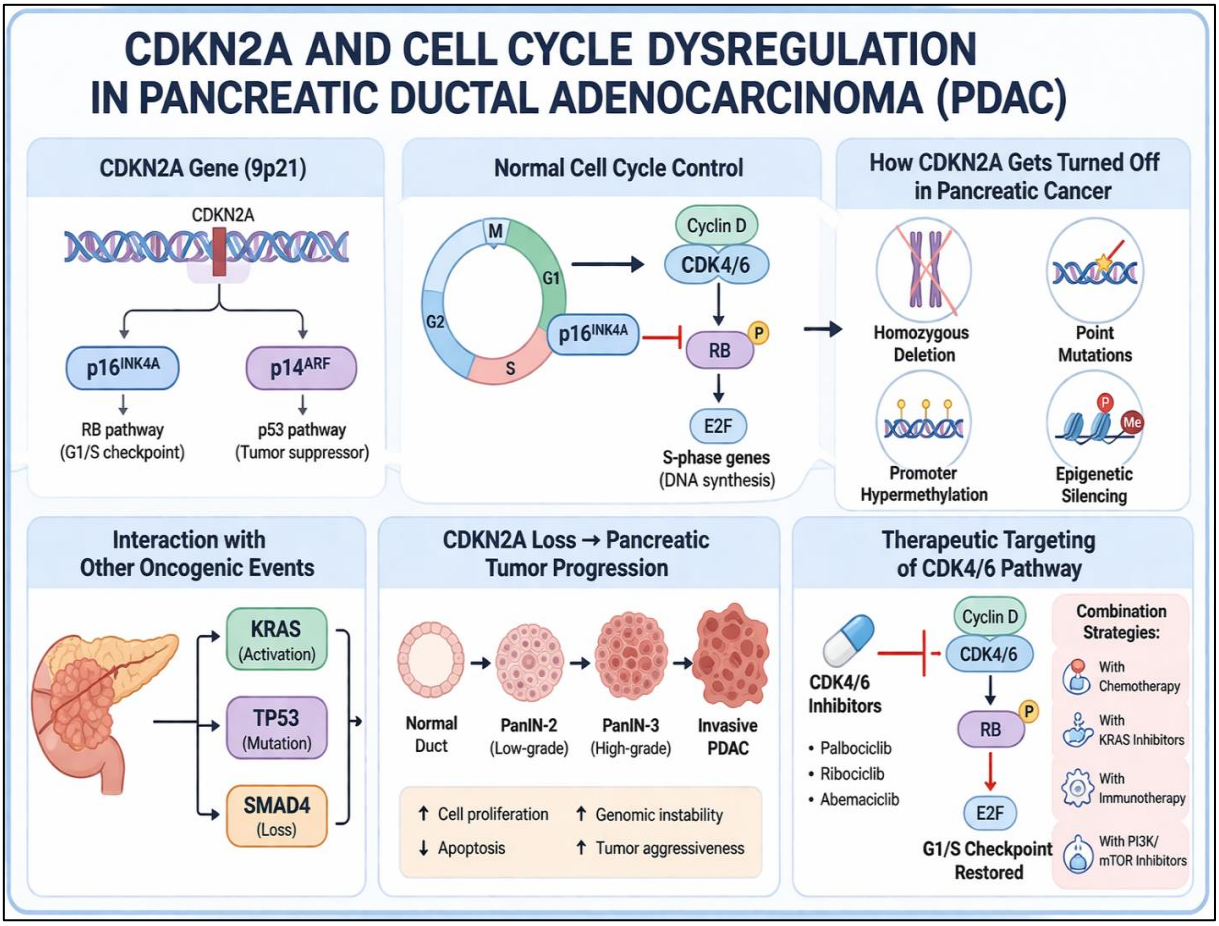

Fig 4 CDKN2A and Cell Cycle Dysregulation

- *Role of CDKN2A in Cell Cycle Control*

The cell cycle is an orchestrated process that guarantees precise DNA replication and division. Progression from one cell cycle phase to another is mediated by cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors, all working in concert to ensure normal cell cycle regulation.

During the G1 phase, CDK4 and CDK6, when combined with cyclin D, are responsible for RB phosphorylation. Phosphorylated RB releases E2F transcription factors, which in turn ensure the transcription of genes that mediate DNA replication and S phase progression.

The function of p16INK4A is to impede this process. It binds to CDK4 and CDK6, preventing them from interacting with cyclin D, thereby inactivating CDK4 and CDK6. This keeps RB active, arresting the cell cycle.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

The loss of CDKN2A function removes the inhibitory effect on CDK4 and CDK6, resulting in the continued phosphorylation of RB and activation of E2F. Consequently, pancreatic cancer cells are able to proliferate normally.

- *How CDKN2A Gets Turned off in Pancreatic Cancer*

There are many ways that the CDKN2A gene is turned off in pancreatic cancer. The most common mechanisms that have been identified include:

✓ *Homozygous Deletion*

This is the deletion of the CDKN2A gene locus on both chromosomes. As a result, the p16 expression is completely turned off. This is a common event in pancreatic ductal adenocarcinoma.

✓ *Point Mutations*

Point mutations of the CDKN2A gene alter the structure and function of the p16 protein. As a result, the p16 is unable to block the activity of CDK4/6.

✓ *Promoter Hypermethylation*

Epigenetic silencing of the CDKN2A gene is also a common event. When the promoter is hyper methylated, the transcription of the CDKN2A is reduced or completely turned off.

Overall, the mechanisms that have been identified above help to explain the high incidence of CDKN2A inactivation that is observed in pancreatic cancer.

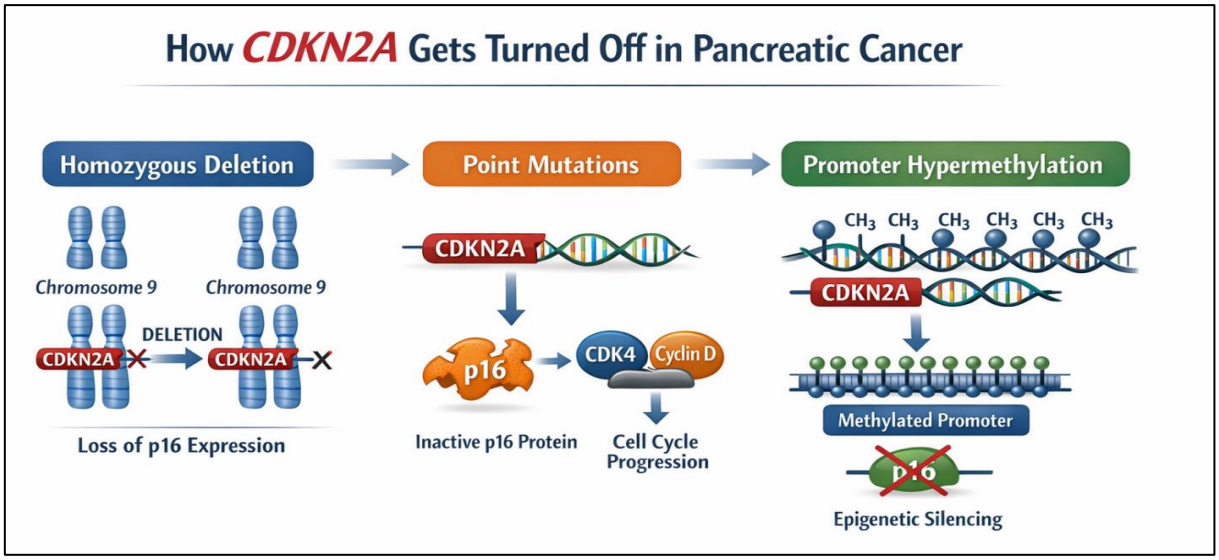

Fig 5 How CDKN2A Gets Turned Off in Pancreatic Cancer

- *How CDKN2A Loss Interacts with Other Oncogenic Events*

Loss of the CDKN2A gene is not an isolated event. In the case of pancreatic cancer, the loss of the CDKN2A is often accompanied by mutations of the KRAS, TP53, and SMAD4 genes.

For example, activation of KRAS mutations activates pathways that drive cells to grow and survive. Normally, this oncogenic stress activates tumor suppressor pathways such as p16 and p53, leading to cell cycle arrest or apoptosis. However, in the absence of CDKN2A, this checkpoint does not occur, allowing unchecked growth caused by KRAS to continue unchecked.

TP53 mutations also continue to compromise cell cycle control and apoptosis, allowing tumor cells to continue to acquire additional genetic changes to become more aggressive tumor cells.

- *CDKN2A and Pancreatic Tumor Progression*

CDKN2A inactivation is an early genetic event in pancreatic tumor development. This inactivation is seen in PanIN-2 and PanIN-3 lesions, which are intermediate to high-grade precursor lesions in pancreatic cancer development. The absence of p16 in these tumor development steps accelerates tumor development from pre-invasive to invasive cancer in the pancreas.

The absence of CDKN2A function also contributes to several characteristics of cancer in pancreatic tumor cells, such as:

✓ Increased cell proliferation
✓ Resistance to apoptosis
✓ Increased genomic instability
✓ Increased tumor aggressiveness

The absence of the RB tumor suppressor function caused by CDKN2A inactivation also helps cancer cells metastasize to other tissues in the body.

- *Therapeutic Targeting of CDK4/6 Pathway*

CDK4 and CDK6 remain active when CDKN2A is lost. This makes CDK4/6 a target for cancer therapy. Researchers have designed several selective CDK4/6 inhibitors to regain control of cell cycle progression. The most investigated CDK4/6 inhibitors are:

✓ Palbociclib
✓ Ribociclib

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

✓ Abemaciclib

These CDK4/6 inhibitors inhibit the kinase activity of CDK4/6. This prevents RB phosphorylation and re-establishes the G1/S checkpoint. CDK4/6 inhibitors have shown impressive results in cancer therapy. For example, in hormone receptor-positive breast cancer, CDK4/6 inhibitors are now a part of cancer treatment regimens.

- *Potential Role of CDK4/6 Inhibitors in Pancreatic Cancer Therapy*

CDK4/6 inhibitors have shown positive results in cancer therapy. However, their effectiveness in treating pancreatic cancer is still under investigation. Preclinical studies indicate that CDK4/6 inhibitors inhibit pancreatic cancer cell proliferation. Moreover, it causes cell cycle arrest. Pancreatic cancer is a complex disease with genetic changes in PDAC. This makes it difficult to achieve positive results with a single drug. Therefore, researchers are trying to develop a combination of CDK4/6 inhibitors with other drugs. Some of these combinations are:

✓ CDK4/6 inhibitors with chemotherapy
✓ CDK4/6 inhibitors with KRAS pathway inhibitors
✓ CDK4/6 inhibitors with immunotherapy
✓ CDK4/6 inhibitors with PI3K or mTOR inhibitors

These combinations are designed to target multiple oncogenic pathways simultaneously to overcome drug resistance.

IV. SMAD4 AND TGF-B SIGNALING IN PANCREATIC TUMOR PROGRESSION

The SMAD4 gene, also known as Deleted in Pancreatic Carcinoma locus 4 (DPC4), is a tumor suppressor gene that regulates the transforming growth factor-beta (TGF-β) signaling cascade. The SMAD4 gene is located on chromosome 18q21. It plays a crucial role in cancer development because it acts as a central intracellular messenger in response to TGF-β receptors. The TGF-β cascade controls various biological responses such as cell growth, differentiation, apoptosis, and extracellular matrix production that are essential in maintaining normal homeostasis in tissues [19,20,34].

The SMAD4 tumor suppressor gene is inactivated in 50-55% of pancreatic cancer cases, making it one of the four main tumor suppressor genes in PDAC alongside KRAS, TP53, and CDKN2A [2,19]. The inactivation of SMAD4 disrupts TGF-β-mediated growth control in cancer cells, leading to tumor progression, metastasis, and poor patient outcomes.[43]

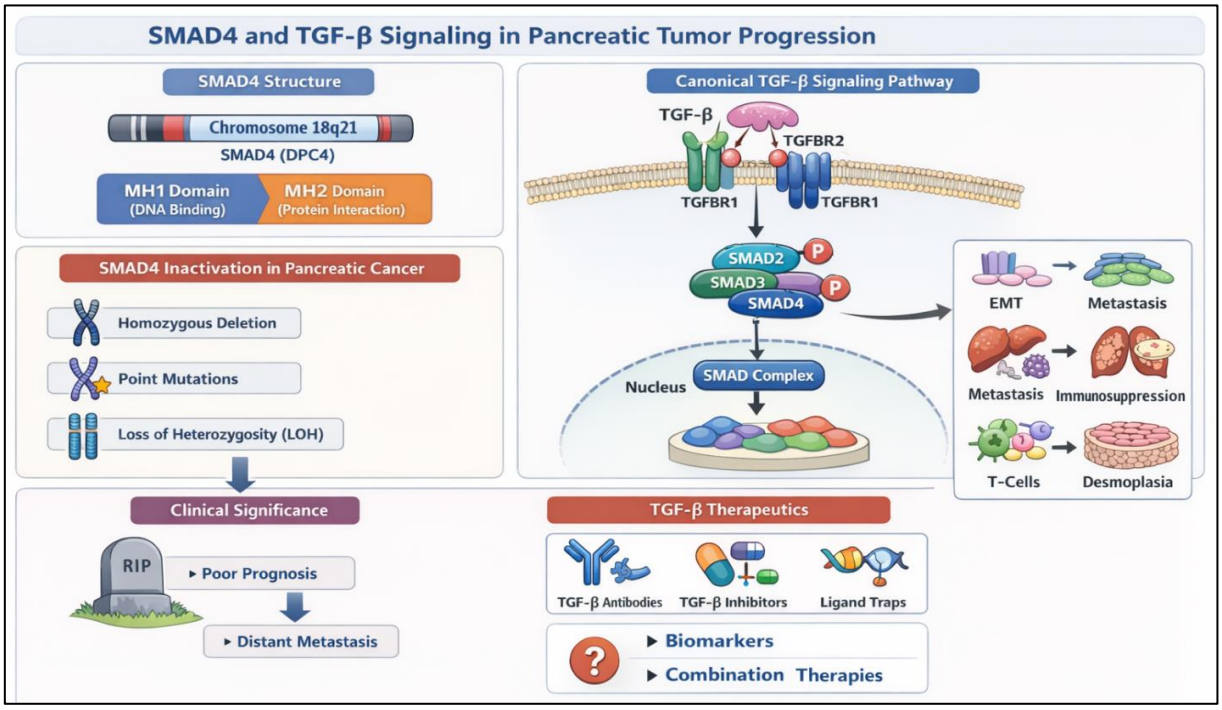

Fig 6 SMAD4 and TGF-B Signaling in Pancreatic Tumor Progression

➢ *Structure and Molecular Function of SMAD4*

The SMAD4 tumor suppressor is part of a family of intracellular signaling proteins known as SMADs that are involved in the TGF-β cascade. There are three main classes of SMADs:

- Receptor-regulated SMADs (R-SMADs) – SMAD2 and SMAD3
- Common mediator SMAD (Co-SMAD) – SMAD4
- Inhibitory SMADs (I-SMADs) – SMAD6 and SMAD7 [19,20]

Of these, SMAD4 acts as a central mediator by integrating the signals from receptor-regulated SMADs, thereby facilitating transcriptional regulation in the nucleus.

The structure of SMAD4 comprises two conserved regions, termed MAD homology 1 (MH1) and MAD

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

homology 2 (MH2). MH1 is responsible for DNA binding, allowing SMAD4 to interact with the promoters of target gene loci. Similarly, MH2 enables SMAD4 to interact with other proteins, facilitating the formation of complexes with other SMADs and transcription factors. Through these domains, SMAD4 plays an important role in transcriptional regulation by modulating the expression of genes that inhibit cell growth, apoptosis, and tissue remodeling.

➢ *Canonical TGF-β/SMAD Signaling Pathway*

The canonical pathway of the TGF-β pathway is initiated when TGF-β binds to type II TGF-β receptor (TGFBR2) on the cell surface. This leads to the recruitment and activation of type I TGF-β receptor (TGFBR1). Subsequently, receptor-regulated SMADs, specifically SMAD2 and SMAD3, are phosphorylated by TGFBR1. SMAD2 and SMAD3, along with SMAD4, function as a heteromeric complex in the canonical pathway.

The complex then enters the nucleus, where it works alongside other factors to determine the expression of target genes of the TGF-β pathway. These genes have a role to play in several important cell processes, such as the cessation of the cell cycle, apoptosis, differentiation, and the production of the extracellular matrix. This way, the TGF-β/SMAD pathway acts as a check on the growth of cancerous cells during the early stages of cancerous tumor formation.

➢ *The Dual Face of TGF-β Signaling in Cancer*

TGF-β/SMAD pathway signaling is characterized by its dual role in cancer, as it may either promote or suppress cancer, depending on the stage of cancer. In the initial stages of pancreatic cancer, the TGF-β/SMAD pathway acts as a suppressor of cancer by regulating the cell cycle, causing the cancerous cells to slow down and die. However, as the cancer progresses and tumor suppressors like the SMAD4 gene mutate, the role of the pathway changes to promote cancer. In the advanced stages of pancreatic cancer, the role of the TGF-β/SMAD pathway may be to:

- Epithelial-Mesenchymal Transition (EMT)
- Invasion and spread of the tumor
- Suppression of the immune response in the tumor microenvironment
- Remodeling of the dense tumor stroma

So, the effect of the loss of SMAD4 is to alter the way the TGFβ pathway functions and to favor the more aggressive behavior of the tumor.

➢ *How SMAD4 Gets Inactivated in Pancreatic Cancer*

There are several different molecular pathways by which SMAD4 dysfunction occurs in pancreatic cancer. Among these:

- *Homozygous Deletion*

The most common mechanism of SMAD4 dysfunction in pancreatic cancer involves the complete deletion of the SMAD4 gene locus located on chromosome 18q21, effectively eliminating the expression of the SMAD4 protein.

- *Point Mutations*

Alterations in a single amino acid or a premature termination mutation of the SMAD4 protein can disrupt its interaction with other SMAD proteins and other transcription factors, thus disrupting the pathway.

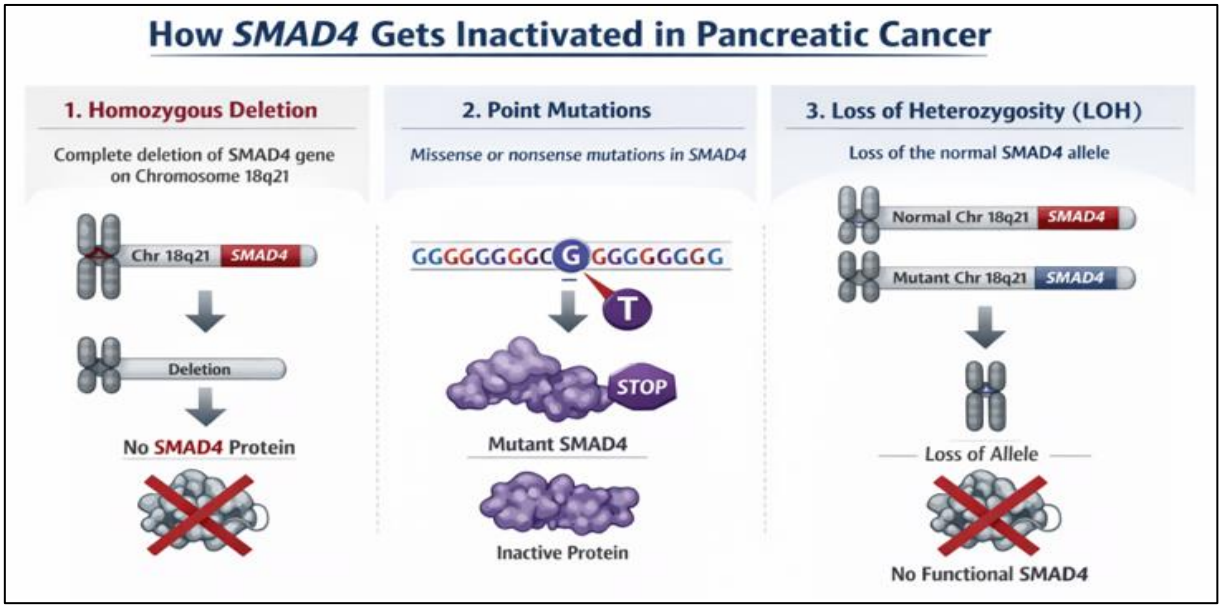

Fig 7 How SMAD4 Gets Inactivated in Pancreatic Cancer

- *Loss of Heterozygosity (LOH)*

Loss of the other copy of chromosome 18q, a common genetic alteration in pancreatic cancer, also results in the dysfunction of the SMAD4 tumor suppressor.

➢ *Impact of SMAD4 Loss in Pancreatic Cancer Progression*

When SMAD4 activity is lost, pancreatic tumors exhibit new characteristics, including aggressive tumor progression and distant metastasis. Without the activity of SMAD4,

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

pancreatic tumor cells do not feel the restrictive force of TGF-β, which limits tumor growth. In addition, tumor invasiveness is increased with the loss of SMAD4 activity. Research has demonstrated that pancreatic tumors lacking SMAD4 exhibit distant metastasis to sites such as the liver, lungs, and peritoneal cavity. In addition, the loss of SMAD4 activity results in the induction of epithelial-mesenchymal transition (EMT). EMT is characterized by the expression of mesenchymal features in epithelial cells, which enhances tumor invasiveness. Another important impact of SMAD4 loss in pancreatic cancer development is the induction of desmoplastic tumor stroma. Tumor desmoplasia consists of dense fibrotic tissue that can inhibit chemotherapy efficacy.

➢ *Clinical Significance of SMAD4 Status in PDAC*

SMAD4 expression status has significant implications in pancreatic cancer development. Research has demonstrated that SMAD4 loss in pancreatic cancer correlates with poor prognosis and reduced overall survival. In addition, SMAD4 expression status has implications for tumor metastasis. Tumors lacking SMAD4 exhibit distant metastasis, whereas those with SMAD4 expression are locally invasive. SMAD4 expression status has implications in pancreatic cancer prognosis.

➢ *Therapeutic Implications of Targeting TGF-β Signaling*

TGF-β signaling plays a critical role in the progression of pancreatic cancer. Therefore, this pathway represents a potential therapeutic target. Several therapeutic approaches have been evaluated to inhibit TGF-β signaling for cancer therapy. These include:

- TGF-β neutralizing antibodies
- Small molecule inhibitors targeting TGF-β receptors
- Ligand traps and antisense oligonucleotides

These therapeutic approaches are intended to counteract the tumor-promoting activity of TGF-β, particularly in advanced-stage tumors where TGF-β plays a key role in metastasis and immune evasion. In the context of pancreatic cancer, these therapeutic agents might be used to improve the efficacy of chemotherapy or immunotherapy by reducing tumor invasion and immune-mediated tumor cell killing.[44]

➢ *BRCA and DNA Damage Repair Pathways in Pancreatic Cancer (PARP Inhibitor Therapy)*

BRCA1 and BRCA2 are two important genes in the DNA damage repair pathway, especially in repairing DNA double strand breaks by homologous recombination. These tumor suppressor genes are responsible for maintaining genomic integrity by ensuring accurate DNA repair. While germline and sporadic mutations in BRCA1 and BRCA2 have long been implicated in the pathogenesis of hereditary breast and ovarian cancer, recent studies have revealed that these genes are also important contributors to pancreatic ductal adenocarcinoma (PDAC) [23,24].

Approximately 5-7% of pancreatic cancer patients have germline mutations in the BRCA1 or BRCA2 genes. There may be additional cases with somatic mutations that affect the HR process. These mutations prevent the process of DNA repair, leading to instability and thereby creating conditions that favor cancer development.

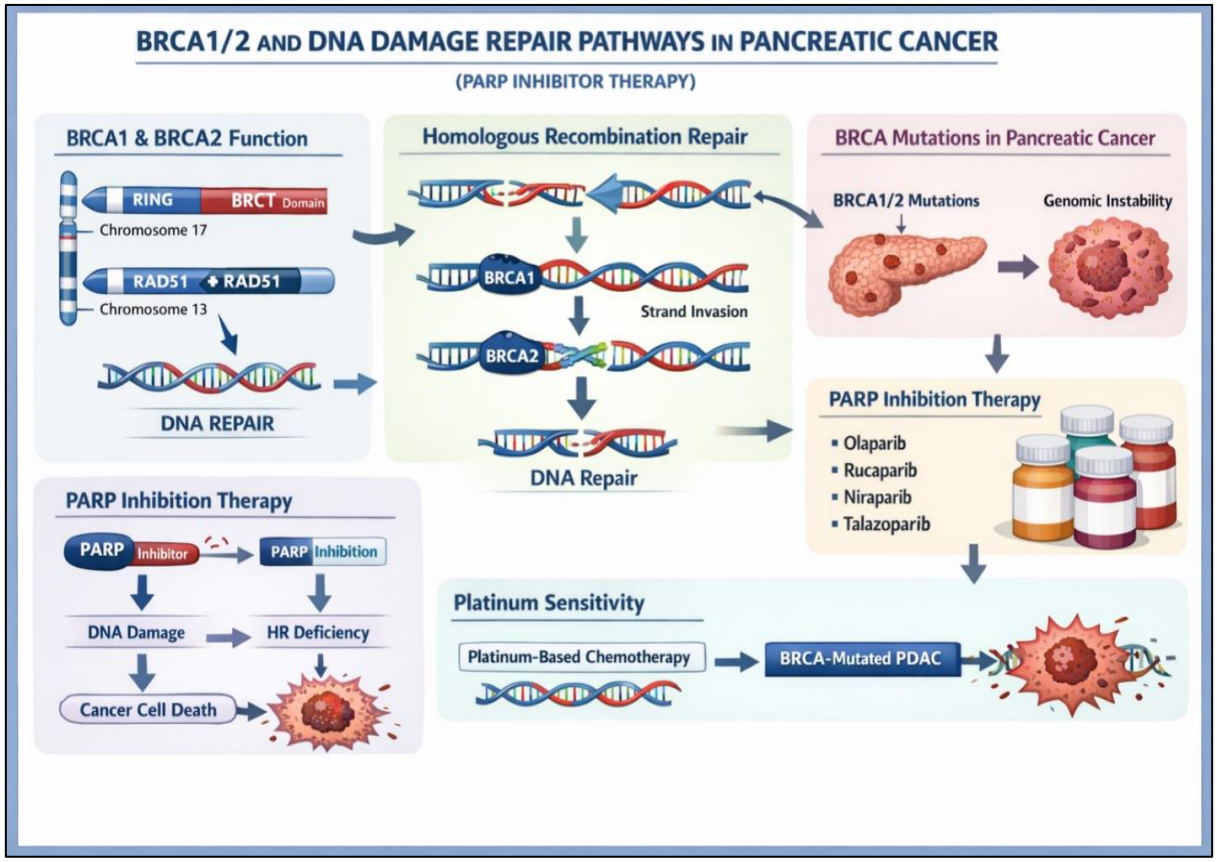

Fig 8 BRCA and DNA Damage Repair Pathways (PARP Inhibitor Therapy)

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

- *Structure and Biological Roles of BRCA1 and BRCA2*

BRCA1 is a large multifunctional protein that plays a role in DNA repair, transcriptional regulation, chromatin remodeling, and cell cycle checkpoint control. It is encoded on chromosome 17q21. BRCA1 has multiple functional regions, which include the N-terminal RING finger domain and the C-terminal BRCT domains. Both regions are important for the interaction of the protein with other proteins that participate in the process of DNA repair.

BRCA2 is encoded on chromosome 13q12.3. It is important in the process of HR as it guides the RAD51 protein to the site of damage. RAD51 plays the role of facilitating the search for homologous DNA sequences and the process of strand invasion, which is important in the accurate repair of double-stranded DNA damage.

BRCA1 and BRCA2 play important roles that involve the regulation of the process of HR. They participate in the regulation of the process of HR, which is important in the accurate repair of DNA.

- *Homologous Recombination DNA Repair Pathway*

One of the most accurate ways of repairing DNA double-strand breaks, which are some of the most lethal lesions that can occur in the genome, is through the homologous recombination repair pathway. When such a break in the DNA strand takes place, the repair machinery is alerted by the activation of the "damage sensor." The initial steps in the repair process are mediated by BRCA1, which facilitates the repair of the ends of the damaged strand and coordinates the repair proteins. The next step in the repair process involves BRCA2, where it facilitates the loading of the RAD51 repair protein on the single-stranded DNA, forming nucleoprotein filaments that enable strand invasion into the sister chromatid. This enables the damaged strand to utilize an accurate copy of the sister chromatid for repair.

- *BRCA Mutations and Genomic Instability in Pancreatic Cancer*

The disruption of HR in cancer cells with BRCA1 or 2 mutations leads to the activation of alternative, less accurate DNA repair mechanisms such as NHEJ. Such alternative DNA repair mechanisms often lead to insertions, deletions, and rearrangements, resulting in an unstable genome. Over time, these genetic changes accumulate and lead to the development and progression of pancreatic cancer. BRCA mutations have significant implications in familial pancreatic cancer syndrome, in which the risk of developing PDAC is greatly increased compared to the general population. Furthermore, cancer cells with BRCA mutations often display a genetic signature termed homologous recombination deficiency, which has significant treatment implications.

- *Synthetic Lethality and PARP Inhibition*

One of the greatest treatment strategies that have emerged from BRCA mutations is that cancer cells with such mutations are susceptible to treatment with PARP inhibitors, which utilize synthetic lethality as a treatment modality. PARP plays an important role in repairing single-strand DNA breaks via the process of base excision repair. When PARP is inhibited, single-strand breaks accumulate and are eventually converted to DNA double-strand breaks upon DNA replication. While normal cells have the ability to repair DNA breaks via HR, cancer cells that have an impaired HR pathway, as in the case of BRCA mutations, cannot repair DNA breaks. This leads to an accumulation of DNA breaks that eventually reach lethal amounts, resulting in the death of cancer cells.

- *PARP Inhibitors in Pancreatic Cancer Therapy*

Several PARP inhibitors are under investigation in clinical trials for cancer types that carry a mutation in the BRCA gene. Some of these are:

✓ Olaparib
✓ Rucaparib
✓ Niraparib
✓ Talazoparib [28,29]

Among these, there are clear clinical benefits to patients with metastatic pancreatic cancer carrying a germline BRCA mutation. The POLO trial was a pivotal trial that demonstrated a significant increase in progression-free survival in metastatic PDAC patients with a germline BRCA mutation who had not progressed on platinum-based chemotherapy. This has now resulted in olaparib being approved as a first-targeted therapy in BRCA-mutated pancreatic cancer patients.

- *Platinum Sensitivity in BRCA-Mutated PDAC*

It is also important to note that BRCA-mutated PDAC patients are more sensitive to platinum-based chemotherapy regimens. Platinum-based drugs are known to cause cross-links in DNA, leading to double-strand breaks in cancer cells. Cells that are already compromised in their homologous recombination repair mechanism are particularly susceptible to this type of damage. This is why BRCA-mutated PDAC patients are known to respond better to platinum-based regimens such as FOLFIRINOX in comparison to those without these genetic mutations [25].

➢ *Integrated Signaling Network: KRAS-TP53-CDKN2A-SMAD4-BRCA in Pancreatic Cancer*

Pancreatic ductal adenocarcinoma (PDAC) develops as a result of the accumulation of various genetic alterations over time. Among the numerous genetic changes that are associated with pancreatic cancer, mutations affecting KRAS, TP53, CDKN2A, SMAD4, and BRCA1/2 are considered to be critical. These genes are not isolated entities; rather, they are part of complex integrated signaling networks that are involved in cell proliferation, cell-cycle regulation, apoptosis, genomic stability, and interaction with the tumor microenvironment. The combined effect of these alterations results in a highly dynamic oncogenic signaling network, thus enabling PDAC to adapt to various forms of stress, such as immune surveillance and chemotherapy.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

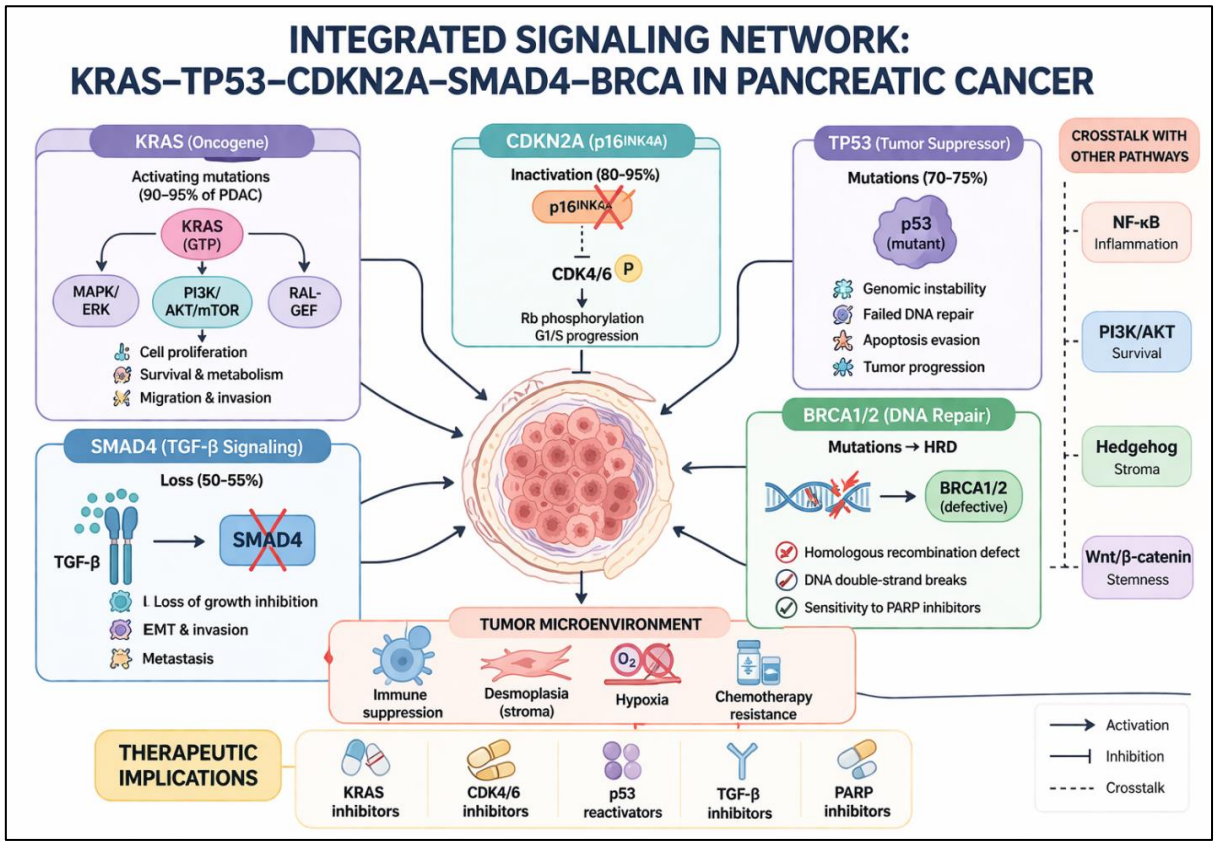

Fig 9 Integrated Signaling Network: KRAS, TP53, CDKN2 A-SMAD4-BRCA

- *KRAS as the Central Driver of Pancreatic Tumorigenesis*

Activating mutations in KRAS are found in about 90 to 95 percent of all cases of pancreatic cancer and represent a very early event in PDAC development [2,3].

KRAS is a gene that encodes a small GTP-binding protein functioning as a molecular switch for a variety of downstream pathways. Signaling pathways activated by KRAS:

✓ MAPK/ERK
✓ PI3K/AKT/mTOR
✓ RAL-GEF [3,31]

These pathways regulate cell growth, survival, metabolism, and migration. Hyperactivation of these pathways by constitutive activation of KRAS causes unchecked growth in cancer cells [3].

However, in normal cells, excessive activation of KRAS results in a variety of protective mechanisms such as cell cycle arrest and apoptosis, primarily mediated by tumor suppressors such as p16 (CDKN2A) and p53 [31].

- *Loss of Cell Cycle Control Through CDKN2A Inactivation*

The gene that encodes the tumor suppressor protein p16INK4A, involved in controlling the G1/S transition by inhibiting the activity of the kinases CDK4 and CDK6, is inactivated in 80-95% of pancreatic cancer cases. The inactivation of CDKN2A removes an important brake on KRAS-mediated cell growth. Without p16INK4A, CDK4 and CDK6 are active kinases, leading to the phosphorylation of the retinoblastoma protein, releasing E2F transcription factors, which in turn activate the transcription of genes required for DNA synthesis and cell cycle progression. The inactivation of CDKN2A thus acts in conjunction with KRAS oncogenic activity to drive cells to uncontrollably divide and form tumors.

- *TP53 Mutations and Genomic Instability*

TP53 gene mutations are found in 70-75% of pancreatic cancer cases and are an important step in the transition of precursor lesions to invasive cancer. The tumor suppressor protein p53 is the main genome caretaker, coordinating the cellular response to stress and DNA damage. It can initiate cell cycle arrest, repair of damaged DNA, apoptosis, and senescence. The inactivation of TP53 means that the cell cycle will progress even in the presence of damaged DNA, leading to uncontrollable cell division and tumor formation. Some mutant p53 proteins even acquire new properties that enhance tumor invasion, metastasis, and resistance to chemotherapy. The inactivation of TP53 means that the tumor evolution process is greatly accelerated, leading to the increased heterogeneity of pancreatic cancer.

- *SMAD4 Loss and the Disruption of TGF-β Signaling*

TGF-β signaling is mediated by the SMAD4 protein, which limits the growth of epithelial cells and enhances differentiation. In pancreatic cancer, the SMAD4 gene is found to be defective in 50-55% of the tumors, thereby disrupting the growth-inhibitory effect of the TGF-β

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

signaling pathway. In addition to this, the disruption of the SMAD4 gene enhances the process of EMT, invasion, and metastasis. In the later stages of cancer, the role of the TGF-β signaling pathway is reversed from tumor suppression to tumor progression, especially after the disruption of the SMAD4 gene.

- *BRCA Mutations and Defects in DNA Repair*

Mutations of the BRCA1 and BRCA2 genes disrupt the process of homologous recombination, which is the high-fidelity process of repairing DNA double-strand breaks. Tumor cells with HRD are highly sensitive to DNA damage agents and to PARP inhibitors, which block alternative DNA repair mechanisms. This explains the rationale for precision medicine approaches to pancreatic cancer, which involve tumors with BRCA mutations that are responsive to targeted agents such as PARP inhibitors or platinum-based agents that target defective DNA repair mechanisms.

- *Crosstalk Between Major Signaling Pathways*

Pancreatic cancer results from a complex interplay of genetic alterations that result in a dense network of interacting signaling pathways. To illustrate this:

- ✓ KRAS signaling activates cell proliferation and reprograms metabolism
- ✓ CDKN2A deletion eliminates critical cell-cycle controls
- ✓ TP53 mutations permit the accumulation of genetic damage
- ✓ SMAD4 deletion increases tumor invasion and metastasis
- ✓ BRCA mutations compromise DNA repair

These alterations combine to produce a tumor microenvironment that supports tumor growth, survival, immune suppression, and resistance to therapy. These pathways interact with other pathways such as NF-κB, PI3K/AKT, and Hedgehog signaling, which further fuels the progression of pancreatic cancer.[45]

- *Implications for Targeted Therapy*

The interplay between these signaling pathways has important implications for the design of targeted therapy for pancreatic cancer. Potential therapeutic approaches include:

- ✓ KRAS inhibitors that target oncogenic signaling
- ✓ CDK4/6 inhibitors to restore cell-cycle controls
- ✓ Agents that restore function to mutant forms of the tumor suppressor protein p53
- ✓ TGF-β pathway inhibitors affecting the SMAD4 pathway
- ✓ PARP inhibitors for tumors with BRCA mutations

The PDAC signaling network is highly adaptive, which means that targeting a single pathway results in resistance. Therefore, combination therapy approaches are being tested to target multiple elements of the oncogenic network.

- *Summary of the Integrated Molecular Network*

To summarize, pancreatic ductal adenocarcinoma results from the cooperative interaction of a number of genetic alterations affecting key regulatory pathways. The integrated KRAS-TP53-CDKN2A-SMAD4-BRCA network regulates key processes in cancer biology, which include:

- ✓ Cell proliferation
- ✓ Cell-cycle regulation
- ✓ DNA damage repair
- ✓ Apoptosis
- ✓ Invasion and metastasis

It is anticipated that a more thorough understanding of these complex pathways of molecular interaction will prove to be of significant importance for the development of new therapies and treatment regimens designed to maximize survival for patients suffering from pancreatic cancer [31-35].

V. CONCLUSION

Pancreatic ductal adenocarcinoma is one of the most challenging cancers to manage due to its aggressive behavior, late diagnosis, molecular complexity, and limited response to conventional treatment. PDAC development and progression is not driven by a single molecular abnormality, but rather by the accumulation and interaction of several genetic alterations and signaling pathways. Among these, mutations in KRAS, TP53, CDKN2A, SMAD4, and BRCA1/2 are important for the promotion of uncontrolled cell proliferation, cell cycle progression, impaired apoptosis, genomic instability, invasion, metastasis and resistance to therapy.

These molecular abnormalities are presented as operating within an integrated network rather than as independent events. KRAS activation leads to the persistent activation of pathways such as MAPK/ERK, PI3K/AKT/mTOR and Ral-GEF, driving tumor growth, survival, metabolic adaptation and migration. Loss of CDKN2A further removes critical cell-cycle control, while changes in TP53 allow damaged cells to escape cell-cycle arrest and apoptosis. Similarly, loss of SMAD4 affects TGF-β signaling and contributes to tumor invasion, metastasis, and stromal remodeling. BRCA1/2 deficiencies impair DNA repair, which opens the door for therapeutic approaches based on synthetic lethality, including PARP inhibition.

The important message emerging from this review is that complexity of PDAC cannot be sufficiently addressed by targeting a single signaling pathway. Oncogenic signaling, loss of tumor suppressors, DNA repair defects and tumor microenvironment interplay to provide alternative mechanisms for cancer cell survival and to contribute to resistance to therapy. The dense desmoplastic stroma also creates an immunosuppressive environment that favors tumor progression and hampers drug delivery. Therefore, more effective therapeutic approaches require better understanding of the pathway crosstalk.

Recent advances of molecularly targeted therapy opened up new possibilities for PDAC treatment. Therapeutic development in KRAS signaling (direct and indirect approaches), CDK4/6 inhibition in tumors with CDKN2A deficiency, efforts to restore mutant p53 function, modulation of TGF-β signaling and PARP inhibition in tumors with

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

BRCA-associated DNA repair defects are important areas of development. But the adaptive nature of PDAC signaling suggests that combination strategies and molecularly guided therapy may be more successful than targeting single pathways alone.

Thus, the future advancement in pancreatic cancer management will rely on the combination of molecular profiling and precision medicine and the identification of individual tumor vulnerabilities. A better understanding of molecular subtypes, signaling pathway interactions, tumor–stroma communication and drug resistance mechanisms may help in the selection of proper targeted and combination therapies. Further research is also required to translate promising molecular targets into clinically effective and durable therapies.

In general, knowledge of the abnormal signaling networks that underlie PDAC provides an important basis for developing more accurate and effective treatments. Despite considerable challenges, further investigation of these interconnected molecular pathways could lead to enhanced early molecular classification, therapeutic selection, treatment response, and ultimately improved clinical outcome for patients with pancreatic ductal adenocarcinoma.

REFERENCES

[1]. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48.
[2]. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371(11):1039–1049.
[3]. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016;2:16022.
[4]. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
[5]. Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. 2012;491(7424):399–405.
[6]. Collins MA, Pasca di Magliano M. Oncogenic KRAS in pancreatic cancer. Nat Rev Cancer. 2012;12(10):697–709.
[7]. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: Mission possible? Nat Rev Drug Discov. 2014;13(11):828–851.
[8]. Canon J, Rex K, Saiki AY, Mohr C, Cooke K, Bagal D, et al. The clinical KRAS(G12C) inhibitor sotorasib drives anti-tumour immunity. Nature. 2019;575(7781):217–223.
[9]. Fakih M, O'Neil B, Price TJ, Falchook GS, Desai J, Kuo J, et al. Adagrasib in KRAS G12C–mutated solid tumors. N Engl J Med. 2022;387(2):120–131.
[10]. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer. J Clin Oncol. 2007;25(15):1960–1966.
[11]. Muller PAJ, Vousden KH. Mutant p53 in cancer: New functions and therapeutic opportunities. Nat Rev Cancer. 2013;13(2):83–96.
[12]. Bykov VJN, Eriksson SE, Bianchi J, Wiman KG. Targeting mutant p53 for efficient cancer therapy. Nat Rev Cancer. 2018;18(2):89–102.
[13]. Lehmann BD, Pietenpol JA. Targeting mutant p53 in human tumors. Cancer Cell. 2012;21(3):319–320.
[14]. Vassilev LT, Vu BT, Graves B, Carvajal D, Podlaski F, Filipovic Z, et al. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. Science. 2004;303(5659):844–848.
[15]. Sherr CJ. Cancer cell cycles. Science. 1996;274(5293):1672–1677.
[16]. Knudsen ES, Witkiewicz AK. The strange case of CDK4/6 inhibitors: Mechanisms, resistance, and combination strategies. Nat Rev Clin Oncol. 2017;14(9):575–588.
[17]. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375(20):1925–1936.
[18]. Dickson MA. Molecular pathways: CDK4 inhibitors for cancer therapy. Clin Cancer Res. 2016;22(10):2380–2385.
[19]. Massagué J. TGF-β in cancer. Cell. 2008;134(2):215–230.
[20]. Ikushima H, Miyazono K. TGF-β signalling: A complex web in cancer progression. Nat Rev Cancer. 2010;10(6):415–424.
[21]. Melisi D, Garcia-Carbonero R, Macarulla T, Pezet D, Deplanque G, Fuchs M, et al. Galunisertib plus gemcitabine vs gemcitabine for untreated pancreatic cancer. Clin Cancer Res. 2018;24(21):5506–5515.
[22]. Herbertz S, Sawyer JS, Stauber AJ, Gueorguieva I, Driscoll KE, Estrem ST, et al. Clinical development of galunisertib (LY2157299), a small molecule inhibitor of TGF-β signaling pathway. Clin Cancer Res. 2015;21(7):1505–1512.
[23]. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017;355(6330):1152–1158.
[24]. Farmer H, McCabe N, Lord CJ, Tutt ANJ, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917–921.
[25]. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434(7035):913–917.
[26]. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381(4):317–327.
[27]. O'Reilly EM, Lee JW, Zalupski M, Capanu M, Park JO, Golan T, et al. Randomized phase II trial of gemcitabine and cisplatin with or without veliparib in pancreatic cancer. J Clin Oncol. 2018;36(15):1375–1382.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug368

[28]. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531(7592):47–52.
[29]. Aguirre AJ, Nowak JA, Camarda ND, Moffitt RA, Ghazani AA, Hazar-Rethinam M, et al. Real-time genomic characterization of advanced pancreatic cancer. Nat Rev Cancer. 2018;18(8):505–518.
[30]. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846–4861.
[31]. Hidalgo M. Pancreatic cancer. N Engl J Med. 2010;362(17):1605–1617.
[32]. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791):607–620.
[33]. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388(10039):73–85.
[34]. Jones S, Zhang X, Parsons DW, Lin JCH, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321(5897):1801–1806.
[35]. Iacobuzio-Donahue CA. Genetic evolution of pancreatic cancer: Lessons learnt from the pancreatic cancer genome sequencing project. Nat Rev Cancer. 2012;12(10):705–713.
[36]. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic developments in pancreatic cancer: Current and future perspectives. Nat Rev Gastroenterol Hepatol. 2018;15(6):333–348.
[37]. Hu ZI, Shia J, Stadler ZK, Varghese AM, Capanu M, Salo-Mullen E, et al. Evaluating mismatch repair deficiency in pancreatic adenocarcinoma. Clin Cancer Res. 2021;27(5):1327–1334.
[38]. Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: Is the undruggable drugged? Nat Rev Cancer. 2020;20(9):533–552.
[39]. Perkhofer L, Gout J, Roger E, Jäger C, Klöppel G, Kleger A. Molecular targeted therapy in pancreatic ductal adenocarcinoma. Nat Rev Gastroenterol Hepatol. 2021;18(11):787–803.
[40]. Hosein AN, Brekken RA, Maitra A. Pancreatic cancer stroma: An update on therapeutic targeting strategies. Nat Rev Cancer. 2020;20(8):457–471.
[41]. Bear AS, Vonderheide RH, O'Hara MH. Challenges and opportunities for pancreatic cancer immunotherapy. J Clin Oncol. 2020;38(16):1825–1835.
[42]. Hezel AF, Kimmelman AC, Stanger BZ, Bardeesy N, Depinho RA. Genetics and biology of pancreatic ductal adenocarcinoma. Genes Dev. 2006;20(10):1218–1249.
[43]. Collins MA, Bednar F, Zhang Y, Brisset JC, Galbán S, Galbán CJ, et al. Oncogenic KRAS is required for pancreatic tumor maintenance. Oncogene. 2014;33(38):4495–4505.
[44]. Makohon-Moore A, Iacobuzio-Donahue CA. Pancreatic cancer biology and genetics. Nature. 2017;546(7657):71–78.
[45]. Hingorani SR, Petricoin EF, Maitra A, Rajapakse V, King C, Jacobetz MA, et al. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. Cancer Cell. 2003;4(6):437–450.