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Article

The Future Prospects of the KRAS Gene and Its Association with Cancer as Predictive Markers

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Abstract: The importance of early cancer detection has grown significantly in recent years due to the widespread prevalence of this disease across various age groups. This article aims to highlight the crucial role of strategies and methods used in the early detection or prediction of cancer, given their vital impact on saving lives and determining appropriate treatment approaches. The KRAS gene has gained prominence in recent years for its role in predicting tumor development before it occurs, as it is one of the most frequently mutated genes in many human cancers. This gene is involved in transmitting cellular signals and regulating the cell cycle, primarily through expressing mutated protein products or altering cellular pathways. Among the most common and frequent KRAS mutations are (G12, G12C, Q61, and G12V), which are observed in cancers such as pancreatic, colorectal, and lung tumors, accounting for approximately 20% of all human cancers. KRAS gene mutations contribute to reinforcing the characteristics of mutated cells and preparing the tumor microenvironment to support their persistence. Several mechanisms by which these mutations evade immune surveillance and distract immune cells from the tumor itself have been identified and studied. In recent years, numerous potential treatment approaches have emerged. Some genetic and molecular therapies have already been approved, while others are in clinical trial stages The emergence of targeted therapies that address specific metabolic pathways of cancer or directly target compounds and molecules involved in disease progression has marked the rise of diagnostic or precision medicine. Various other approaches and strategies are still under investigation, aiming to achieve a comprehensive cure for cancer.

Keywords: genes, KRAS, immune evasion, cancer, mutations

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1. Introduction

Genes are units or segments of DNA that make up the genetic system in any living organism. They function to store and direct information for the production of proteins, thereby controlling the formation of our bodies [1]. Humans possess many genes inherited from their parents, amounting to more than 23,000 genes, located in specific regions of the cell called chromosomes [2]. Numerous variations or mutations can occur in these genes, leading to changes in the sequence of nitrogenous bases in the DNA molecule. As a result, the structure of the protein produced from the expression of the mutated gene is altered, which in turn affects the physiological and medical state of the body. This often marks the beginning of cancer development.

The tremendous advancements and discoveries in genomics have enhanced our understanding of the mechanisms behind the occurrence of many diseases, including rare ones. This significant progress in the field of human genomics has led to the development of innovative therapeutic strategies for disease prevention [3]. One of the most common diseases linked to the human genetic structure is cancer — the dilemma of our modern

age. Many genes are susceptible to errors in the sequence of nitrogenous bases during DNA replication in cell division. These changes are called mutations, some of which are hereditary and accumulate over generations, increasing the likelihood of developing certain types of cancer. Over 95 genes have been identified in the human genome as being susceptible to such mutations [4], [5], [6], [7].

Among these well-known genes in the scientific community is the KRAS gene — an abbreviation for Kirsten Rat Sarcoma, first discovered in a viral oncogene in rats. This gene is capable of producing a protein that carries signals regulating cell division and proliferation, and under certain conditions, it can become oncogenic [8], [9], [10]. Therefore, it is considered one of the genes that regulate the cell cycle by expressing its products, most notably the KRAS protein, which plays a role in transmitting signals from outside the nucleus to the inside to initiate cell replication and division [11]. KRAS is one of the most mutation-prone genes, with one in every seven human cancer cases associated with a mutation in this gene [12]. Any disruption or malfunction in this gene due to mutations can lead to changes in functional pathways, causing the emergence of indicators of cancer onset and progression. Many studies have demonstrated a strong correlation between KRAS mutations and tumor evasion from the immune system.

2. Materials and Methods

These mutations can potentially serve as diagnostic or predictive markers for the presence or progression of cancer, especially in individuals who carry such mutations, such as those leading to colorectal cancer . Due to the structural nature of the KRAS gene and the presence of active mutations in many human cancers — along with its smooth surface lacking binding sites for small molecule drugs — this gene was considered undruggable for the past three decades.

However, the advent of immunotherapy, combined with some KRAS inhibitors, has recently shown efficacy. Current efforts are focused on exploiting therapeutic approaches to treat patients with pancreatic and colorectal cancers resulting from KRAS mutations. This involves using inhibitors of gene expression products or preventing the production of lactic acid in cancer cells. Among these therapeutic strategies targeting gene products are selective inhibitors approved by the United States Food and Drug Administration (USFDA), such as Adagrasib and Sotorasib, for treating various types of cancer. There is an urgent need to establish a global strategic stockpile of drugs that target KRAS or its products.

3. Results and Discussion

Intracellular Signal Transduction

The KRAS gene is a member of the RAS family, which is involved in various aspects of regulating cell growth and division through the gene expression of protein products. These proteins, in turn, transmit signals from growth factor receptors to a cascade of signaling proteins, including transcription factors and cell cycle proteins [13]. (Figure 1)

KRAS mediates signal transmission between active and inactive proteins along multiple intracellular pathways by activating protein kinases via the active signal regulator phosphoinositide. This signaling pathway has been identified in fibrosarcoma [14], where KRAS regulates intracellular signaling within cancer cells and their surrounding environment, particularly in pancreatic ductal adenocarcinoma cells. Here, it facilitates intercellular signal exchange, promoting the growth and proliferation of cancer cells and enhancing their energy production capacity, thereby accelerating tumor development [15].

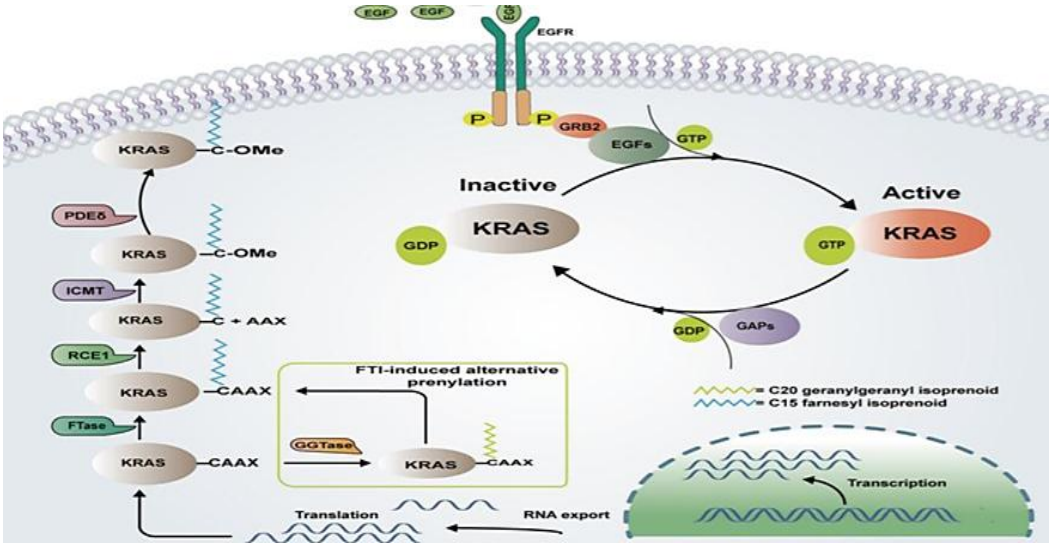

Figure (1). illustrates the signal transduction process within the cell by the KRAF gene, facilitated by post-transcriptional modifications with the assistance of several enzymes [16]

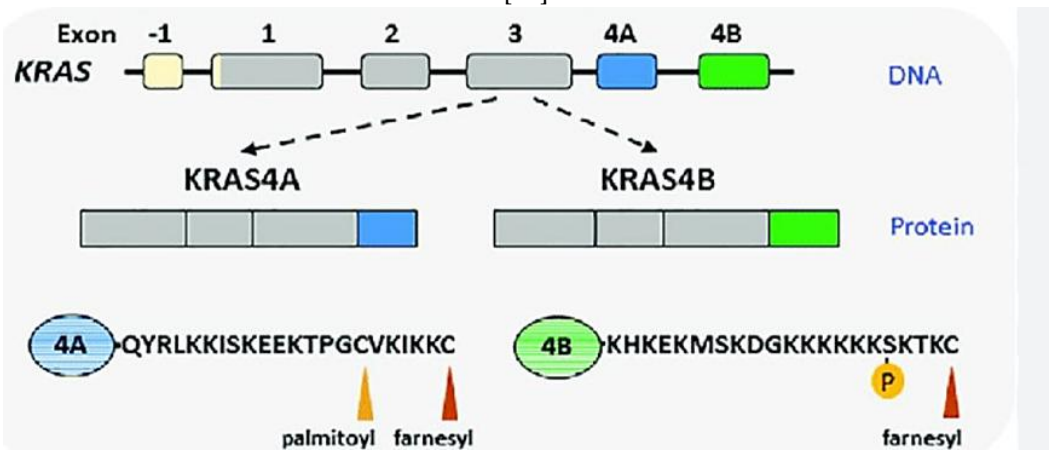

Figure (2). showing the structure of the KRAS gene [17]

The PI3K-AKT-mTOR pathway has been identified within the KRAS gene as a key signaling route, playing a critical role in cell life cycle regulation, differentiation, and programmed cell death (apoptosis), and having a significant impact on the development of disease resistance [18]. When the KRAS gene is activated, it stimulates the PI3K-AKT pathway by binding to its specialized subunits. This activation is facilitated through PIP2 (phosphatidylinositol 4,5-bisphosphate), which provides energy to the pathway after being converted into PIP3 (phosphatidylinositol 3,4,5-trisphosphate) [19].Figure (2).

Numerous active molecules operate along this pathway during KRAS activation and intracellular signal transmission, adding to the complexity of the signaling mechanism. The presence of a large number of phosphorylated proteins and lipids associated with cell migration highlights the gene's influence on cell adhesion mechanisms and cytoskeletal formation [20]. Additionally, KRAS regulates phosphoinositide signaling through the activation of a pathway known as PLC (phospholipase C) [21].

KRAS Mutations Leading to Cancer

The KRAS gene possesses distinct characteristics and is considered the most common and the primary suspect among the RAS gene family in the development of human cancers [22]. Numerous mutations have been identified in the KRAS gene, with the most prevalent being Q61, G12D, G12V, and G12C, commonly found in pancreatic, lung, and colorectal cancers [23].

The oncogenic KRAS gene was first discovered in Kristen Rat Sarcoma Virus (K-Ras), and among the well-known RAS genes (HRAS, NRAS, and KRAS), KRAS is the most

frequently studied [24]. Recently, the integration of genomic data with cancer epidemiology has revealed that approximately 16–20% of human cancers harbor a RAS mutation, with KRAS mutations representing 11–14% of all malignant tumors [25]. Modern discoveries in genetic engineering and biochemistry have laid a strong foundation for the direct targeting of KRAS-specific mechanisms, including the G12C mutation in lung cancer, leading to the development of initial inhibitors and therapies [26].Several KRAS mutations significantly influence tumor characteristics and interact with other oncogenic mutations. Studies have shown that KRAS mutations are intricately linked with other driver mutations such as TP53 and alterations identified in TCGA, involving complex signal exchanges across tumor cell pathways [27]. Furthermore, KRAS mutations in codons 13 and 22 are commonly found in colorectal cancer (CRC), where they contribute to the activation of tumor-promoting pathways [28]. It is noteworthy that KRAS mutations occur across a variety of human cancers with varying frequencies and follow different sub-pathways within the tumor microenvironment [29].

There is also a mutation pattern difference between smokers and non-smokers; for instance, G12C is more prevalent in smokers, whereas G12D is more common in non-smokers in gastrointestinal cancers (30). Since the KRAS gene and its protein products regulate the cell cycle, the activation of mutations impairs the KRAS protein's function, leading to cellular transformation and increased resistance to receptor-targeted therapies [31].

Some studies have classified KRAS mutations into two groups based on binding affinity. The high-affinity group includes G12D, G12V, G12A, G12R, and G12H, while the low-affinity group includes G12C, G12D, Q61L, and G12K. These mutations exhibit varying sensitivity to targeted therapies [32]. Among recent studies focusing on KRAS mutations in ovarian cancer, a metabolic pathway was identified in serous-type ovarian cancer that can be targeted using BRAF inhibitors and specific enzymes [33]. In certain studies, involving the analysis and isolation of oncogenes, KRAS mutations were found to be the most frequent, followed by P53 protein mutations in the studied cancer tissues [34]. Additionally, the STK11 gene and an ECH-associated protein were found at a low frequency (<1%) [35].The oncogenic KRAS gene appears in approximately 30% of large-cell lung cancer cases. In these patients, the GTPase enzyme is active, especially in the presence of the KRAS p.G12C mutation, which occurs in about 40% of lung cancers in smokers. This mutation can be targeted using specific inhibitors that prevent the mutated protein from binding to GTPase, thereby inhibiting tumor growth [36]. Since this cancer type accounts for roughly 80% of all lung cancers, particular focus has been placed on KRAS due to its high frequency in non-small cell lung cancer (NSCLC), making it a potential early diagnostic marker for this type of cancer [37].

Tumor Microenvironment (TAM) and KRAS Mutations

In general, KRAS mutations not only instill tumor cell characteristics and promote a suitable environment for cancer growth, but they also contribute to forming a tumor microenvironment (TME) that supports proliferation. Additionally, they influence the immune cells of the body, thereby protecting the cancerous tissue from immune system attacks [38]. It has been found that within the tumor microenvironment, inflammatory cells occupy immune lymphocytes along with other factors, such as cytokines and proteins, which directly penetrate immune cells and mediate pathways activated by KRAS signaling [39].

The high activity of these mutations and the resulting increase in intracellular signaling directed to the cell nucleus by KRAS leads to increased secretion of immune interleukins, especially IL-6 and IL-5, which enhances inflammation within the tissue and consequently promotes tumor growth and progression [40].Some studies have shown that the interleukins secreted in the tumor environment of pancreatic cancer can worsen and accelerate tumor development [41]. Recent studies also indicate that tumor-promoting

factors secreted in the lung tumor microenvironment (TAM) interfere with the function of T immune cells, thereby creating a favorable environment for cancer progression [42].

KRAS mutations occur in pancreatic cancer cells, where they form a suppressive tumor microenvironment (TAM) that inhibits immune cell activity by preventing the infiltration of T cells and myeloid-derived suppressor cells (MDSCs), making the function of tumor inhibitors more difficult [43]. Furthermore, KRAS mutations can alter the internal tumor environment and affect the functional behavior of cancerous cells, making them a potential target for studying and controlling tumor determinants, in addition to their inflammatory role within the TAM [44].

Mouse models have shown that the K-ras allele activates in the bronchial epithelial cells during lung tumor development, accompanied by a strong immune response, macrophage accumulation, and a significant increase in inflammatory cell stimulation within the tumor environment [45]. Some studies have reported that mutated KRAS genes contribute to the formation of TAM by increasing the production of chemical compounds involved in generating an inflammatory environment, enhancing IL-1α production, and activating the IKKB/NF-κB signaling pathway [46]. The production of these compounds in the cancer environment is associated with enhanced immune resistance and immune checkpoint evasion (ICB), which leads to a deeper understanding of common mutations [47]. There is also an interactive relationship between KRAS and TP53 mutations, forming a combined mutation that can be exploited to target immune checkpoints within the tumor environment. Therefore, RAS is not the sole gene responsible for most cancers [48].

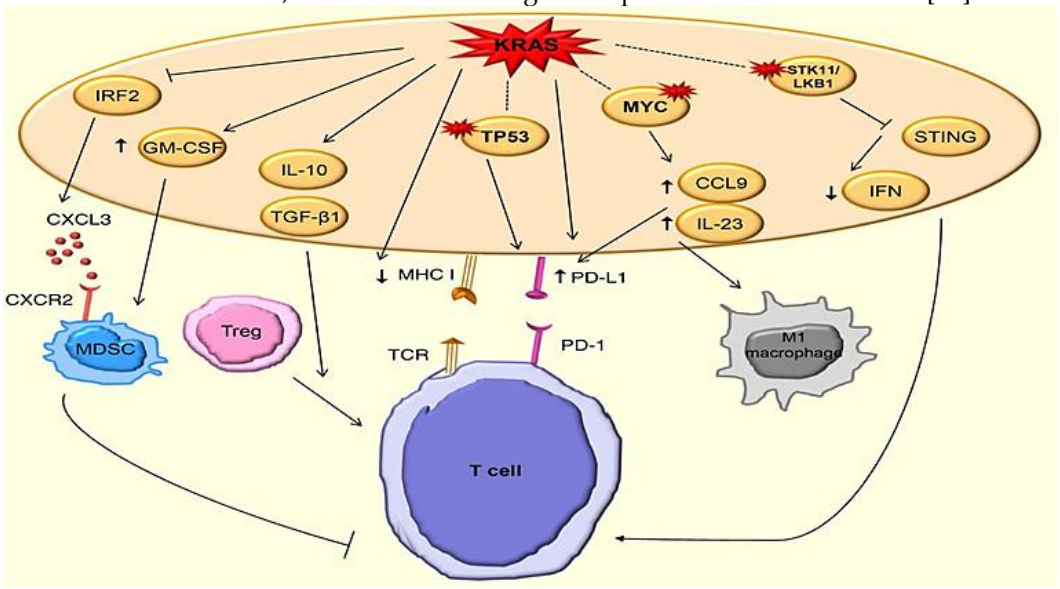

Figure (3). shows the simultaneous KRAS and TP53 mutations and their effect on immune modification in the internal environment of the cancerous tumor [49].

Long-term effects may arise due to KRAS mutations and abnormalities in the tumor's TAM pathways, which affect the tumor's immune defense by disrupting immune checkpoints [50]. (Figure 3) High regulation of signals from cancer cells with a high mutation rate is often observed, along with the ability to regulate tumor tissue characteristics, as seen in lung cancer (NSCLC) and pancreatic cancer. These mutations are known to act as active immune inhibitors in some types of cancer [51]. However, immune checkpoint inhibitors (ICB) can be made more capable of recognizing cancer cells and reducing tumor immune evasion by identifying the genes responsible for this evasion and limiting their activity through direct targeting with inhibitors [52].

One promising approach to reduce immune evasion and make the tumor microenvironment suitable for gene inhibitor activity is the use of DNA methylation inhibitors. Low doses of the drug Decitabine have been used, resulting in tumor growth

inhibition along with increased immune cell infiltration into the tumor microenvironment and tumor tissues in a mouse breast cancer model [53].

KRAS and Immune Evasion

Immune evasion and the lack of immune response have many causes, including dysfunction in the immune system, defects in immune cell-producing stem cells, and possibly reduced sensitivity of T-cells. Cancerous tumors can be the main cause of this as mutated cancer cells work to evade the body's immune system through various factors like cytokines or immune inhibitors [54].

KRAS mutations are among the most significant causes of immune resistance in cancer. Immune evasion leads to an increase in abnormal mutated gene loci associated with the tumor [55]. The tumor's internal environment is penetrated by macrophages and myeloid-derived suppressor cells, in addition to the main immune cells. However, signals from KRAS mutated genes in the tumor microenvironment (TAM) play a role in modifying and suppressing immunity [56]. Some immune evasion mechanisms have been identified for certain types of cancer, such as small-cell lung cancer. Among the mechanisms that tumors use to evade immunity are reducing white blood cell infiltration into mutated tissue and preventing the activation of checkpoint inhibitors by changing the cytokine secretion ratios [57]. KRAS mutations mediate immune evasion by altering the basic characteristics of the cancer cells themselves and modifying the secretion of cellular mediators that prevent immune factors from entering and spreading [58]. In mouse models, RAS mutations have been shown to inhibit tumor-fighting T-cells and increase resistance to applied treatments. (59) A synergy between various mutations has been observed to create a resistant internal environment that helps maintain tumor growth. Additionally, DNA repair genes are inhibited through the expression and production of the PDL-1 protein [60].

Immune evasion is one of the causes that ultimately leads to metastasis and the spread of cancer cells throughout the body due to the continuous evolution of the TAM within the tumor and the occurrence of mutations that enhance signals that limit or suppress immune factors. Cancer cells adopt mechanisms of constant change or reduce antigens, thus escaping the immune system [61]. The tumor's microenvironment plays a crucial role in cancer development as it forms a medium for immune cells with multifunctional roles, alongside signals from mutated DNA capable of continuously changing this environment. This complicates the tumor's cellular structure [62]. This suggests that the possibility of using immunotherapies is complicated due to the continuous modification of immune components within the tumor tissue that help it escape the patient's immune system [63]. Studies have shown that the expression of mutated genes increases disease resistance by creating signaling networks inside the cancer's TAM [64]. RNA plays a key role in immune response due to its involvement in gene expression by regulating protein formation and interacting with DNA that mediates immune interactions within malignant cells [65].

miRNA can contribute to cancer cell evasion and spread. It also plays a role in either inhibiting or activating the tumor by regulating immune cell functions within the tumor microenvironment, thus contributing to cancer development [66]. Thus, immune evasion has become a widespread phenomenon in most cancers, and phenomena like metastasis and tumor recurrence can be attributed to this. The continuous change in TAM within cancerous tissues is due to the release of signals from mutated genes that lead to immune cell evasion by reducing antigens on the surfaces of cancer cells [67].

Potential Treatment Methods

One of the most frequent pathways in most human cancers is the KRAS pathway, which controls many secondary pathways through various mutations that regulate signals entering and exiting the cell. Therefore, making KRAS or one of its gene expression products a target for targeted cancer therapies is possible [68]. One promising therapeutic approach in addressing KRAS mutations is immunotherapy, which enables immune cells to target and eliminate the tumor. However, this type of treatment still faces the obstacle

of immune evasion by cancer cells [69].Some inhibitors have proven effective by designing selective inhibitors for the KRAS gene or targeting one of its pathways. Among these inhibitors is the one targeting KRASG12C mutation, and research has indicated encouraging results that open the door for this therapeutic approach [70]. Such therapeutic strategies have targeted other mutated genes in the RAS family, in addition to improving recovery and outcomes for patients with KRAS-mutated cancers [71].KRASG12C has been actively targeted, leading to a shift in research methods aimed at obtaining clinical treatments. Indeed, two molecular inhibitors, Adagrasib and Sotorasib, have been approved for KRAS mutations in small-cell lung cancer. Progress has been made in this field, especially in targeting the RAS family and their gene products in various cancers, both directly and indirectly [72].

It has been found that inhibiting proteins produced by the mutated KRAS genes is challenging. This has led to a shift towards combining different therapeutic methods, such as combining immunotherapy with genetic inhibitors and targeting metabolic pathways that supply tumors with the necessary growth signals [73]. Despite the emergence of these inhibitors, resistance and rapid adaptation to the drugs used have prompted researchers to develop new drugs to overcome these barriers, such as targeting the tumor microenvironment and internal pathways and combining immunotherapy with targeted therapy to address immune evasion [74].One of the reasons for high mortality in rectal cancer is the abundance of branching signals from mutated genes, leading to rapid tumor development. It has been found that when one of the primary pathways is targeted using chemotherapy, alternative secondary pathways are quickly activated, preventing control over the disease [75].

One therapeutic method in mutated skin cancer (BRAF) involves using inhibitors within the gene expression pathway, such as Oncoprotein proteins. These inhibitors block these pathways and thus prevent or delay the growth of cancerous tumors [76]. However, after prolonged treatment, a reactivation of a group of tumor cells, especially melanocytes in the skin, has been observed [77]. Other therapeutic methods include using targeted therapy, which directly applies to metabolic pathways inside the tumor tissue, or molecular therapy by adding a specific inhibitor to slow or block the metabolic pathway within the tumor microenvironment [78].Direct targeting of compounds and molecules that contribute to disease growth and development is a strategy of molecular therapy or personalized medicine, where treatment is built from proteins or molecules specific to the cancer in a given individual. However, this approach remains very complex, awaiting further research in this area [79]. Furthermore, the widespread use of traditional chemotherapy has shown many dangerous side effects, as well as weak treatment responses due to the activation of many mutations, including KRAS mutations in patients with advanced lung cancer [80].

Although designing or manufacturing treatments targeting cancers formed by KRAS mutations is challenging, significant global efforts are underway to target tumor networks and metabolic pathways. Moreover, combining immunotherapy and genetic inhibitors represents a promising avenue in fighting cancer [81]. Among the recent innovative treatments is gene therapy with NPRL2, a gene that inhibits tumor growth by blocking gene expression in cancer cells, thus stopping the cell cycle. These types of treatments are still under development in the hope of achieving revolutionary treatments in cancer medicine [82].Recently, there has been testing on enhancing gene therapy using immune checkpoint inhibitors to combat pancreatic cancer caused by the KRASg12d mutation by designing and programming immune cytokines in the living body of mice and then transferring them to humans. This showed promising results in treating the mutation and reducing tumor growth while extending survival [83].The rapid development of KRAS-targeted drugs has revealed facts about this gene, such as the high similarity between the protein products of the RAS family and GTP, in addition to the absence of binding sites for drugs targeting KRAS mutations [84]. To overcome these obstacles, weaknesses such as

the metabolic process within the tumor microenvironment have been exploited by identifying compounds that target tumor immune cells instead of cancer cells using specialized inhibitors, thus weakening the tumor's ability to grow and spread. [85], [86], [87], [88].

Therefore, the dilemma facing oncologists is the emergence of drug resistance, which continuously arises due to the behavior of various mechanisms, including resistance mutations in the targeted protein and even in other branching pathways in the tumor structure [89], [90]. Thus, it is currently difficult to conclusively determine the existence of a curative treatment for cancer due to the lack of pockets or binding sites for any therapeutic molecules on the surfaces of mutated genes or proteins related to KRAS. However, recent discoveries have identified binding sites on the KRASG12C protein, and an inhibitory compound has already been designed and experimentally tested as a potential drug [91].

4. Conclusion

Hormone therapy plays a crucial role in female cancers, where hormones or their inhibitors are used as drugs targeting specific types of female cancers, such as estrogen and progesterone inhibitors as strategies for treating uterine and ovarian tumors. These have shown high effectiveness against these cancers. Recent research has opened new horizons for research and development to discover new treatments, one of which is the use of immune cells in pancreatic cancer by reengineering T-cells to attack and inhibit cancer cells. An experimental vaccine has been developed to enhance immune cells in lymph nodes, showing a rapid immune response to T-cells in preliminary trials .

In an effort to create a therapeutic strategy for mutant adenocarcinoma lung cancer, chemotherapy was combined with immunotherapy by targeting metabolic pathway weaknesses on one hand and utilizing immune checkpoints to isolate and combat tumor tissue . KRAS is among more than 600 known oncogenes, and it is the most prominent and most common in human cancers, accounting for over 25% of human cancers, as it produces smooth protein products upon gene expression from its mutations. It is difficult to bind any therapeutic molecule to its surfaces, presenting a challenge that is still hard to overcome . In advanced research, nanotechnology has been combined with molecular therapies for diagnosing and treating tumors by using nanoparticles to carry and deliver therapeutic molecules to specific proteins and DNA sites in cancer tissues .Recent discoveries in cancer diagnosis and treatment have taken a rapid pace toward achieving a comprehensive treatment for cancer, which now threatens both young and old alike.

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