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Molecular Mechanism of Cell Signaling Pathways of Cancer Cells in Forward and Reverse Mutation: A Perspective Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author NSH conceptualized the research work. Authors NSH and RTT performed the methodology. Author NSH did formal analysis. Authors NSH and RTT did data curation. Author NSH wrote original draft. Authors NSH, MSH, MAR, RSC, MAA, MIH and RTT did funding acquisition. Authors MSH, RSC and MIH did data visualization. Authors MAR, MAA and RTT did software analysis. Author RTT supervised the study. Author RTT investigated the study. Author RTT wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

One of the most dreaded diseases is cancer whose biological process has long been the focus of scientific inquiry. Changes to normal cellular pathways that result in uncontrolled cell growth and proliferation are widely accepted as the primary cause of cancer. It is known as cancer cells' forward mutation, unchecked proliferation and few pathways contribute to cancer development. Including PI3K-Akt pathway EGFR, PI3K/AKT/mTOR, Notch, NF-κB, Ras/MAPK and Wnt/β-catenin are essential for cancer development. Certain cancer forms' genesis and progression are attributed to several cell signaling pathways including the Ras/MAPK and PI3K/AKT/mTOR pathways. In breast, prostate, colorectal, lung and ovarian cancers, the PI3K/AKT/mTOR pathway is often activated, promoting cell survival, proliferation and metastasis. Lung, colorectal, thyroid, and pancreatic cancers often exhibit activation of the Ras/MAPK pathway, which controls cell proliferation, differentiation and survival. It is extremely uncommon but under some circumstances, cancer cells can undergo reverse mutation which returns the mutant gene to its normal phase. It has been observed that despite notable advancements in the field of cancer biology, the intricate relationship between forward and reverse mutations in the formation of cancer is still poorly understood with no prior study having thoroughly investigated their combined processes. This article aimed to provide an investigation of the primary biological processes behind both reverse and forward mutation upon examining the molecular mechanisms underlying both forward and reverse mutation.

Keywords: Cancer cell; cell signaling pathways; forward mutation; reverse mutation; protein molecules.

1. INTRODUCTION

Throughout the world, cancer is a serious public health issue [1]. Approximately ten (10) million individuals receive a cancer diagnosis each year [2]. In underdeveloped countries, where the prevalence of cancer has reached pandemic levels, more than half of them reside [2]. Researchers have discovered many cancer stages, suggesting that several gene alterations have a role in the genesis of cancer [3]. A sequence of progressively occurring gene mutations that alter cell activities causes cancer [3]. Cancer generally causes cellular relationships to break down and essential genes to stop working [3]. This disruption causes aberrant cell division and affects the cell cycle [3]. However, developmental problems result from mutations in important cellular genes [3-6]. It is one of the primary mechanisms via which proto-oncogenes might transform into their oncogenic form [7]. Cancer results from the gradual accumulation of many mutations over many years of a person's life [7]. Cancer is essentially a genetic illness, and it is widely known that inherited abnormalities in DNA repair pathways raise one's lifelong chance of developing the disease [8]. Overgrowth of cells, apoptosis avoidance and metastasis can all result from mutations in vital genes [9]. Uncontrolled cell proliferation and the capacity to infiltrate other tissues are the two primary characteristics of cancer cells, which are the outcome of genetic and epigenetic modifications. Gene copy number variation (CNV), loss of heterozygosity (LOH), genomic instability, and genetic mutations are examples of genetic alternations [10]. Conversely, histone alterations, DNA methylation and loss of imprinting (LOI) are examples of epigenetic modifications [10]. Forward mutation of cancer cells is a term used to describe the transformation of normal cells into cancerous ones [11]. Several cell signaling pathways are involved in the forward mutation of cancer cells, which transforms regular cell proliferation into aberrant cell growth and ultimately, cancerous cells [12].

The pathways include the PI3K-Akt pathway, the Ras protein-related pathways and the Src/FAK gene signaling system, among others [12]. These pathways may get altered, leading to various forms of mutated genes and ultimately cancerous cells [12]. However, while most research is about this forward mutation of cancer cells, a new phenomenon is termed reverse mutation [13]. Interestingly, it has been revealed in several studies that, under some situations, cancer cells can be transformed back into normal cells [13]. Broadly speaking, cancer reversion is the process of cancer cells losing their malignant traits and gaining the phenotypic traits of normal cells by a biological reprogramming mechanism that suppresses malignancy [13]. According to a

source, cancer reversal was first noted in 1907 [14]. The subject matter was the spontaneous differentiation of ovarian teratomas into a normal somatic cell lineage [14]. It is crucial to comprehend reverse mutations as they can pave the way for new methods to correct genetic abnormalities in cancer cells, potentially resulting in advanced therapies that can stop cancer growth and restore normal cellular activities [15]. Moreover, it appears that although cancer cell reverse mutation is a very complex process, more research on it can be useful in further research and cancer treatment. This review paper summarises the molecular mechanism of forward mutation and reverse mutation in cancer cells. Cell signaling pathways of forward mutation and some of the molecules which are responsible for reverse mutation are also included here. This will also include the clinical consequences of using the reverse mutation mechanism of cancer cells.

2. FORWARD MUTATIONS IN CANCER

Cancer is a genetic condition [16]. It is brought on by modifying the genes that regulate cell division and growth. Sections of DNA called genes contain the information needed to generate one or more proteins [17]. It has been discovered that more than hundreds of genetic and DNA variations, also called mutations, alterations, or variants, assist in cancer development, growth, and spread [18]. The progression from a normal cell to a malignant cell is primarily propelled by the buildup of genetic damage, such as activated proto-oncogenes and deactivated tumor-suppressor genes [19]. In the case of human colon and lung tumors, the development has been linked to the activation of Ras oncogenes and the inactivation of various suppressor genes, including p53 [19]. About the clonal hypothesis of oncogenesis, a tumor is said to originate from a single cell. Moreover, a strong correlation exists between the formation of tumors and the prevention of programmed cell death, also known as apoptosis, which grants cells immortality [20]. Tumor expression of angiogenesis and angiogenic factors suggests that these molecules are important for the genesis and growth of malignancies [20].

Fig. 1 shows the common pathway of transformation of normal cells into cancer cells. While inactivating tumor suppressors removes important negative regulators of signaling, mutations that turn cellular proto-oncogenes into oncogenes can hyperactivate signaling pathways [21]. In an experiment, the PI3K-Akt and Ras-ERK pathways are examined to show how these changes dysregulate signaling in cancer and result in many of the traits that distinguish tumor cells [21].

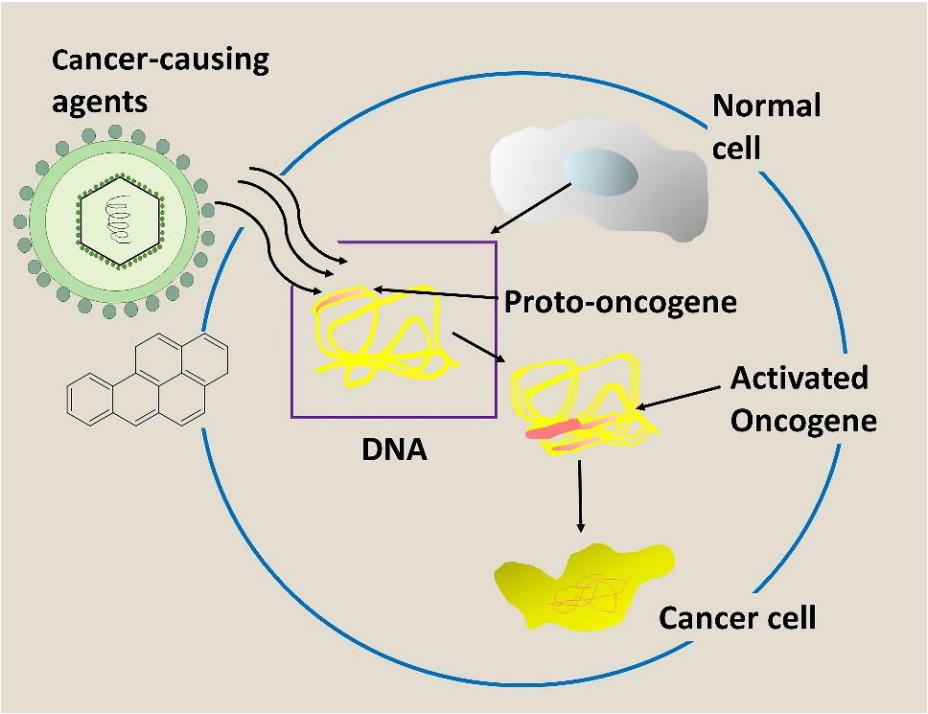

Fig. 1. Transformation of normal cells into a cancer cell.

3. CELL SIGNALING PATHWAYS OF CANCER CELLS IN FORWARD MUTATION

Complex genetic and epigenetic alterations in a single cell or a cluster of cells result in cancer [22]. These changes lead to the over-proliferation of malignant cells, interfere with "normal" cell function and evade processes that normally regulate their growth, division and migration [22]. Many of these "disruptions" correspond to certain signaling pathways within cells [22]. Three main pathways of cancer cell signaling are the Src/FAK gene signaling pathway. The Ras protein-related pathways and the PI3K-Akt pathway [22].

3.1 Src/FAK Gene Signaling Pathway in Cancer Cell

More and more evidence points to Src's significant involvement in tumor cell invasion, particularly when it comes to its interactions with FAK (focal adhesion kinase) [22].

Localized to cell-matrix adhesions, Src and FAK are nonreceptor tyrosine kinases that mediate integrin signaling [22]. After integrin engagement, Src interacts with FAK pTyr397 through the SH2 domain, causing FAK to undergo autophosphorylation at Tyr 397 and recruit Src to active FAK [22]. Many stimuli, such as integrin contact, cause FAK to autophosphorylate on a specific tyrosine (Y) residue, Y397 [23]. This results in the creation of a high-affinity binding site for the SRC homology 2 (SH2) domain of multiple proteins, including the upstream SRC kinase itself [23]. Understanding the role that signaling through elevated phospho-FAK plays in the behavior of cancer cells is crucial [23]. The enhanced complex formation between FAK and its SH2-containing proteins may result from phosphorylation of Y397 or Y925. SRC, SHC, phospholipase Cγ (PLCγ), growth factor receptor bound protein 7 (GRB7), GRB2, p120RHOGAP and p85 (a phosphatidylinositol 3-kinase regulatory component) are a few examples [23]. Phosphorylation at the FAK-Y925 phospho-acceptor site, which is unique to SRCs, can result in FAK exclusion from focal adhesions [23]. FAK is also thought to be connected to the RAS–MAPK (mitogen-activated protein kinase) pathway through this location [23]. This pathway is linked to adhesion alterations brought on by SRC that result in an epithelial-mesenchymal transition [23]. Memorandum ruffles and podosomes, or invadopodia, are dynamic protrusions often seen in cancer cells and implicated in the extracellular matrix's breakdown [22]. Src and FAK are present in both of these structures. In some distinct epithelial malignancies, particularly invasive cancers, both Src and FAK show increased expression [22].

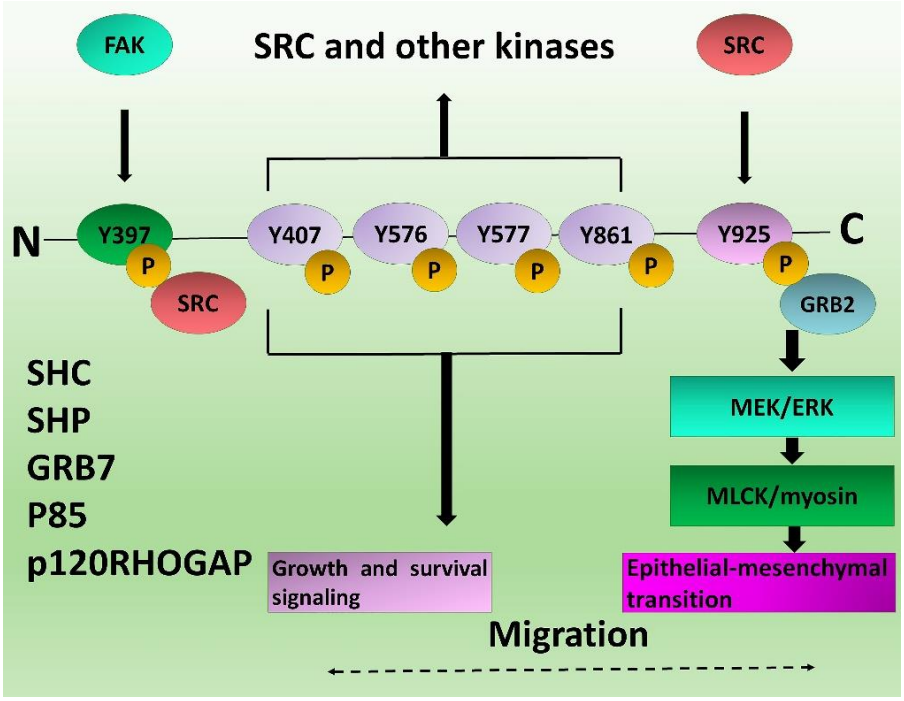

Fig. 2. Tyrosine phosphorylation of FAK controls subsequent signaling processes.

3.2 Ras Protein-related Pathways in Cancer Cell

More than 30.0 % of malignancies and 90.0 % of pancreatic, lung, and colon cancers have been shown to have a Ras gene mutation [24]. The Ras proteins, K-, H-, and N-Ras are molecular switches that are involved in the cascade of cell process regulation (proliferation and cell division) [24]. They are activated by binding to GTP [24]. The aetiology of certain human malignancies has been demonstrated to be significantly influenced by mutations in the Ki-ras gene, which are present in 95.0 % of pancreatic tumors, 50.0 % of colon tumors, and 30.0 % of lung adenocarcinomas respectively [25]. A significant portion of malignancies has hyperactivated RAS–RAF–MEK–ERK signaling pathways, most often as a result of activating mutations in the KRAS, NRAS and BRAF genes [26]. One of the most common oncogenic changes found in cancers produced in animals and humans alike is the RAS pathway [25]. Wild-type RAS proteins interact with guanine nucleotide exchange factors to replace GDP with GTP in response to upstream signaling molecules, producing an activated protein conformation [25]. Interaction with GTPase activating protein inhibits RAS activity by stimulating the protein's GTPase activity, which returns GTP to GDP and returns RAS to its dormant state [25]. RAS mutations bind the protein in the active GTP-bound conformation and suppress GTPase activity [25]. For this reason, when RAS is activated, a series of intracytoplasmic proteins, including RAF and MEK, are phosphorylated. These proteins are ultimately in charge of regulating cell division, proliferation, and survival [27]. Mutant RAS* causes cells to become malignant by keeping them in the active state and ignoring signals to the contrary [28]. For instance, in colorectal cancer, the EGFR ligand, an external stimulus, binds to and activates the EGFR receptor on the cell membrane to start the process [27].

Subsequently, the ERK1/2 transcription factor activator is activated by the sequential downstream activation of RAS, RAF, and MEK [27]. In the end, this system causes metastasis, angiogenesis, differentiation, apoptosis, and cell proliferation [27].

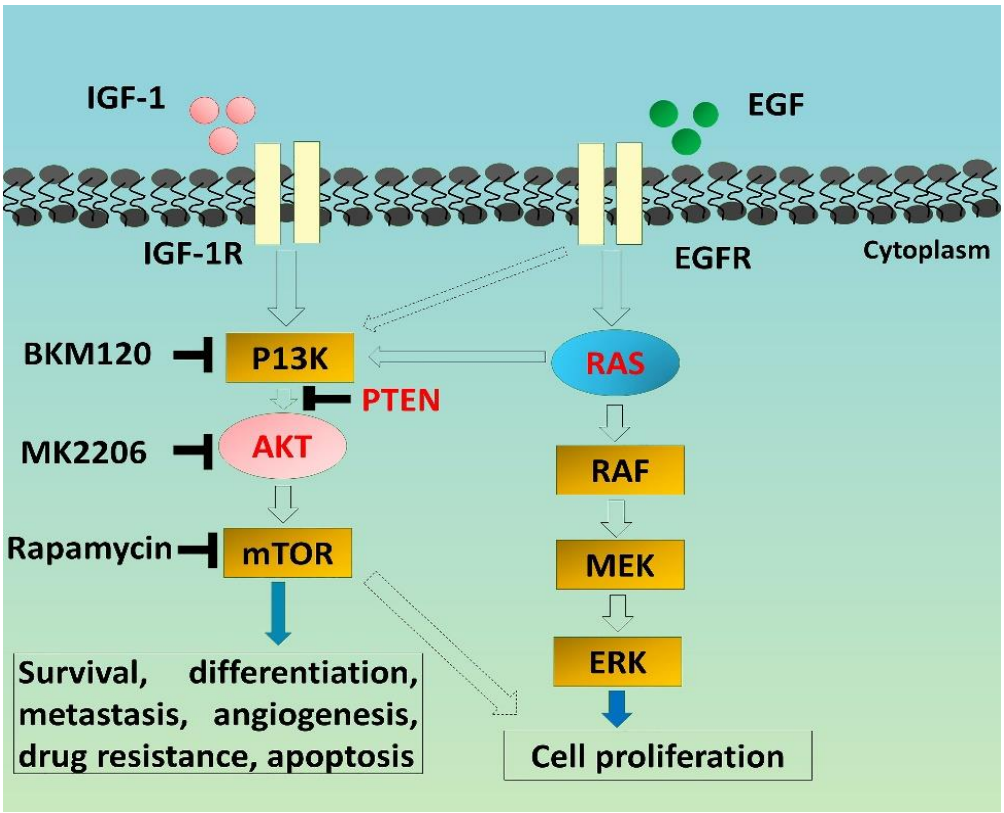

Fig. 3. Downstream activation of RAS, RAF, and MEK in colorectal cancer.

3.3 PI3K-Akt Pathway in Cancer Cell

In human malignancies, the PI3K/Akt/mTOR signaling pathway is frequently active and is implicated in cell survival, growth, and proliferation [29]. A common finding in cancer is dysregulated mTOR activation, which is a step in the carcinogenesis process [29]. As a part of the two protein complexes, mTOR complex 1 and mTOR complex 2, that regulate different cellular processes, mTOR interacts with other proteins [29]. For example, in human colorectal cancer, over-activation of mTOR signaling is frequently observed and is strongly linked to the development, spread and resistance to treatment of the disease [30].

Through lowering the amounts of cell cycle proteins, the PI3K/AKT/mTOR pathway prevents cell growth [30]. The TOR signaling pathway is then implicated in several cellular functions, including polarization, proliferation and expansion of cells [30]. Major roles in colorectal cancer are played by three subfamilies: MAPK/ERK, c-jun amino-terminal or stress-activated protein kinase (JNK orSAPK) and MAPK14 [30]. The growth, differentiation, survival, and death of colorectal cancer cells are all regulated by ERK/MAPK [30]. The ERK pathway influences colon cancer cells' ability to proliferate, migrate, and invade [30]. The mTOR signaling pathway plays a role in the multi-stage control of VEGF-mediated angiogenesis throughout the development of colorectal cancer [30]. AKT interacts with nitric oxide (NO) through a variety of phosphorylation processes during neoangiogenesis in colorectal cancer [30]. This interaction activates endothelial nitric oxide synthase, which generates gas and controls endothelial cell migration and angiogenesis via AKT signaling [30]. Therefore, the cloning, differentiation, invasion, and metastasis of tumor cells are all tightly regulated by the mTOR pathway [31].

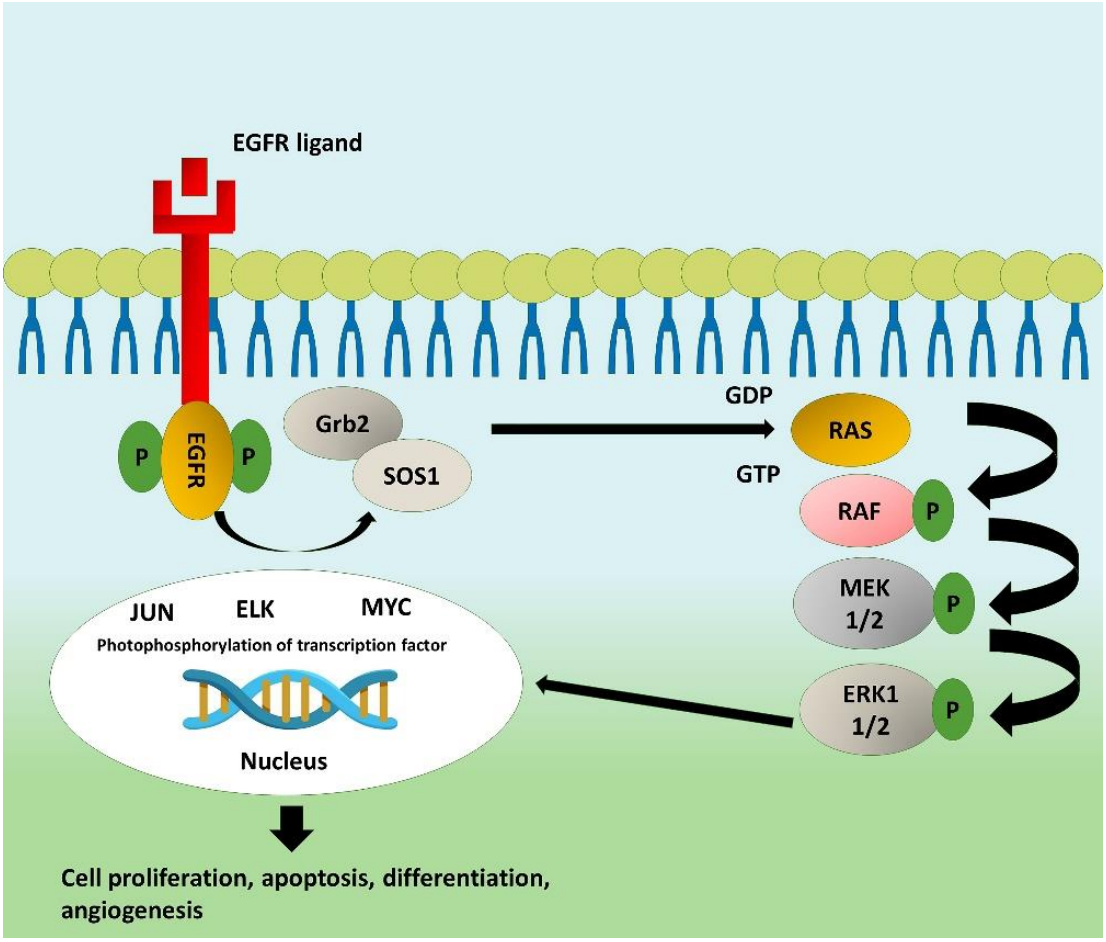

Fig. 4. PI3K/AKT/mTOR signaling pathway in colorectal cancer.

4. FORWARD MUTATION AND REVERSE MUTATION OF CANCER CELL

According to research, microbiological investigations have investigated the varied sensitivity of wild-type sequences to different mutagens through forward mutations that transform them into mutant forms and reverse mutations that restore the wild-type sequences from the mutant forms [11]. Forward mutations have been discovered to lead to genes becoming harmful or losing their regular function, thus speeding up the onset of cancer [32]. On the other hand, back mutations also referred to as reverse mutations, can revert previously altered genes to their original genetic sequence and function, potentially reversing the malignant phenotype [32]. In established malignancies, reverse mutation is an uncommon occurrence that is unlikely to have a major impact [33]. However, researchers must first understand reverse mutations to pinpoint the underlying DNA repair processes and perhaps even target them.

5. UNDERPINNINGS OF REVERSE MUTATION IN CANCER BIOLOGY

Cancer has been traditionally viewed as a genetic disorder with numerous mutations fueling its advancement [34]. Recent evidence suggests that the abnormal metabolism in cancer cells is not just a characteristic of cancer but could be the root cause of the tumor [34].

5.1 Discovery of Reverse Mutation of Cancer Cells

The first recorded case of cancer reverse processing was in 1907 [14]. In this case, ovarian teratoma underwent spontaneous differentiation into a typical somatic cell lineage [14]. Later on, a number of these instances have been sometimes reported in mammals as well as in plants, newts, and other various creatures [14]. The notion of "the development of methods that would direct the differentiation of embryonal carcinoma cells to benign forms as a logical means of controlling this type of cancer" was offered by Pierce in 1959, along with an emphasis on the critical function that the cell microenvironment plays [35]. The notion of "cancer reversion," which describes how malignant cells might regain their normal phenotype in response to a particular microenvironment, was first popularized as a result of these findings [35]. Brinster verified Pierce's theory in 1974 [36]. The "reversion" strategy in cancer research has not been thoroughly investigated, despite these experimental findings [37]. Possibly due to the epistemological instruments required for simulating reversal processes [37].

5.2 Concepts of Molecular Mechanisms of Reverse Mutation

It was believed that tumorigenesis was irreversible. Nonetheless, it has been demonstrated that cancer cells in normal microenvironments spontaneously transform back into nonmalignant cells [13]. Broadly speaking, cancer reversion is the process of cancer cells losing their malignant traits and gaining the phenotypic traits of normal cells by a biological reprogramming mechanism that suppresses malignancy [13]. Three theoretical theories of cancer cell reversion were introduced through an experiment [38]. These are (i) a single event model, in which the restoration of a crucial event from the initial transformation causes the tumor to revert; (ii) a bypass model, in which the tumor is revered by multiple events focusing on signaling pathways other than the original transforming pathway; and (iii) a comprehensive model, in which the tumor reverts the cancer cells and causes them to change from their initial normal state to a new non-malignant state [38]. For instance, it has been demonstrated that in primary tumors, cyclin A1 methylation was negatively correlated with the presence of p53 mutations and that in HNSCC cell lines, cyclin A1 forced expression strongly induced the expression of wild-type p53 [39]. There are known reverse mutations in the BCR-ABL fusion gene in some leukemia cases, and these mutations may lead to remission in certain situations [40].

5.3 Molecular Mechanism of Reverse Mutation in Cancer Cells

When a second mutation neutralizes the effects of the first, reversion takes place. Phenotype is the particular subject of reversion [41]. The original base sequence is seldom recreated. They're referred to as real revertants [41]. A second base change typically neutralizes the effects of the previous base change [41]. The revertants in this instance are known as second-site regressors. The term "suppressor mutation" refers to the second mutation [41]. Though the evidence is subtle but conclusive, several layers

of molecules/events, including transcription factors, microRNAs, alternative RNA splicing, post-transcriptional and post-translational modifications, proteomics, genomics editing tools, and chemical biology approaches, offered hope for manipulating cancer cells to revert to a normal cell phenotype [42]. The development of normal cells into cancerous cells is triggered by various factors, such as chromosomal instability, loss of heterozygosity, accumulation of genetic mutations, DNA methylation, and intron retention (particularly in TSGs) [43]. Additionally, it involves evading immune surveillance, metabolic irregularities, defects in DNA repair mechanisms, uncontrolled cell proliferation, new blood vessel formation, disruption of post-transcriptional and post-translational modifications (PTMs), the influence of the tumor microenvironment, and changes in the composition of the extracellular matrix [43]. Tumor reversion has been linked to several biological mechanisms and molecules. Some of the molecules are Translationally Controlled Tumor Protein 1 (TCTP1), SIAH E3 ubiquitin protein ligase 1 (SIAH1), Tumor suppressor activated pathway 6 (TSAP6), MYC etc. [42]. It has been discovered that TCTP dysregulation in breast cancer causes the tumor to restructure and start to form duct-like structures that give the appearance of normal breast tissue [44]. This mechanism is similar to that of SIAH-1 in that it suppresses the malignant phenotype [44]. It causes cellular rearrangement by inhibiting TCTP production by anti-sense cDNA or short interfering RNA molecules [44]. Tumor reversion, then, can be characterized at the molecular level not only as the reversal of malignant transformation but also as a biological process in and of itself, involving a cellular reprogramming mechanism that overrides genetic alterations in cancer by initiating an alternate pathway that suppresses it [44]. In colorectal cancer (CRC), SIAH1 overexpression resulted in the inhibition of malignant cell invasion and cellular proliferation [45]. On the other hand, CRC cell invasion and proliferation are both enhanced by SIAH1 suppression. In U937 cells, SIAH1 overexpression not only caused apoptosis but also tumor reversal [45]. Transnationally, TSAP6 regulates TCTP secretion and occasionally functions as a cell detoxifier [38]. TSAP binds with TCTP, according to the Y2H test. TSAP6 is a key gene involved in the process of tumor reversion, as evidenced by its activation and tumor suppressor behavior following TP53 activation [38]. TPT1 gene was also detected in tumor revertants produced from U937 cell lines [38]. Tumors are transformed by MYC inhibition back into normal or dormant cell states [46]. This mystery was examined in cases of osteosarcoma and lymphoma when the whole tumor was effectively removed by MYC blocking [46]. Tumor cells from MYC-induced hepatocellular and breast cancer were interesting, but they went into dormancy [46]. Moreover, dormant cells returned to a malignant state after MYC reactivation [46]. Tumor reversion was also observed upon MYC suppression in several malignancies, including T and B cell leukemia and lymphoma, squamous cell, and mesenchymal cancers [47].

According to research, stability is the most important characteristic of real cancer reversion to a nonmalignant state, and stable reversion techniques are preferable to those that generate differentiation [48]. DNA flaws must be repaired by a sophisticated system that is in place to monitor and manage mutations in the genome [49]. While mutations are necessary for evolution, a rise in their frequency can have negative effects [49]. Genomic instability and cancer in organisms are therefore more likely to occur when errors occur in DNA repair pathways [49]. For example, the activation of the important tumor suppressor protein p53 might cause genes involved in DNA repair to be expressed, which raises the possibility of reverse mutations [50]. A study found that a certain phenotype confers susceptibility to PARP inhibitors and platinum therapies in BRCA-associated malignancies, including those of the breast, ovarian, pancreatic, and prostate [51]. Resistance is mediated by somatic reversion mutations that restore BRCA1/2 function; these mutations have only been found in malignancies linked with BRCA [51]. Here, PARP (poly (ADP-ribose) polymerase) is an enzyme involved in DNA repair, and BRCA1/2 (BRCA) are genes that help repair DNA and maintain genome stability [51].

6. SOME CASES THAT CONFIRM THE REVERSE MUTATION OF CANCER CELLS

In a study, it has been demonstrated that in BRCA1/2-mutated cancer cells, restoration of BRCA1/2 functions as a result of additional BRCA1/2 mutations has been identified as a mechanism of acquired resistance to cisplatin and poly (ADP-ribose) polymerase inhibitors [52]. This suggests that tumor suppressor gene mutations that cause sickness can also be genetically reversed in cancer cells if doing so would benefit the cells' survival ability [52].

According to different research, one important cause of resistance to therapy with Poly (ADP-ribose) polymerase (PARP) inhibitors in BRCA-associated malignancies is the presence of reversion mutations, which return the BRCA gene to its wild-type activity [53]. A case report from separate research detailed a patient with BRCA2 pathogenic variant breast cancer who was resistant to olaparib, a PARP inhibitor, and whose cancer genomic profile suggested the mutation was a reversion [54]. So, it is clear that some of the genes of the cancer cells can reverse and form the wild-type variety of the cell.

7. THERAPEUTIC IMPLICATIONS

The ability to offset the effects of oncogenic mutations through reverse mutations offers a special possibility that might revolutionize cancer therapy approaches [55]. The therapeutic consequences of cancer cells reverting to a less aggressive, differentiated state, or undergoing reverse mutation, are noteworthy [56]. This phenomenon casts doubt on the conventional somatic mutation hypothesis of cancer, which holds that genetic alterations are the only factor causing cancer [56]. The identification of reverse mutations implies that various techniques affecting gene expression and cellular signaling pathways can be used to encourage cancer cells to return to a less aggressive state [57]. This may result in novel treatment approaches that aim to reverse the malignant phenotype of cancer cells by targeting the molecular mechanisms responsible for cancer cell reversion [36]. Furthermore, comprehending the processes of reverse mutation may offer insights into the first phases of cancer development, facilitating more efficient early detection and therapy [13].

8. FUTURE RECOMMENDATION

It is necessary to research the molecular mechanisms behind cancer cell reversion such as cellular signaling, epigenetic modifications, and gene expression control. This might assist in determining precise goals for treatment measures. Researchers need to investigate the possibility of using CRISPR-Cas9 and other gene editing technologies to cause reverse mutations intentionally. Clinical studies should be conducted to determine if cancer cell reversion treatments are effective for treating different forms of cancer. This might assist in evaluating the viability and security of these methods for use with human patients. Strong evidence of the advantages and possible hazards of these therapies might be included in the design of these studies. Enhancing treatment procedures and providing useful real-world data might also come from recording and evaluating case studies of patients who have received these medicines. More research and experiments are necessary in this field as only a limited number of studies have been conducted.

9. CONCLUSION

Researchers have long been interested in the molecular basis of cancer, one of the most feared illnesses. It is widely accepted that the primary cause of cancer is the disruption of regular biological processes, which results in uncontrollable cell division and development. It is termed as the forward mutation of cancer cells. In some specific conditions, the reverse mutation of cancer cells happens and it leads the mutated gene to be back to normal phase although it is a very rare condition. It has been found that besides various reasons a variety of mutations can cause cancer cells to alter normal cellular pathways for proliferation. Some of the main pathways that are mutated and play a vital role in forming cancer cells are the Src/FAK gene signaling pathway, the Ras protein-related pathways, and the PI3K-Akt pathway. Besides there are some molecules that can lead the reverse mutation process under some conditions and some of the molecules are molecules are Translationally Controlled Tumor Protein 1 (TCTP1), SIAH E3 ubiquitin protein ligase 1 (SIAH1), Tumor suppressor activated pathway 6 (TSAP6), MYC etc. All the information provided in this article was based on scientific evidence. By observing the molecular mechanism of both forward mutation and reverse mutation it can be concluded that, as the molecular mechanisms are very complex, more and more research and clinical trials are needed to restrict the growth of cancer cells.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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