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The Potential Role of circRNAs Action on Classic Pathways of Signal Transduction PI3K/AKT in Treatment of Pancreatic Cancer

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Abstract: Cancer is a highly complex disease characterized by diverse clinical manifestations and intricate etiology, involving DNA impairment, RNA dysregulation, protein dysfunction, and other contributing factors. The progression, invasion, angiogenesis, and metastasis of cancer are regulated by a multitude of pathways and agents that influence crucial cellular processes like apoptosis, cell survival, and gene expression. Among these pathways, the PI3K/AKT signaling pathway has emerged as a pivotal player, interacting with various intracellular agents including proteins, microRNAs (miRNAs), and circular RNAs (circRNAs). CircRNAs, in particular, form intricate networks that play essential roles in tumor development, transforming previous perspectives on cancer incidence, growth, metastasis, as well as diagnosis, prognosis, and treatment. A deeper understanding of these intricate intracellular interactions holds the potential for improved cancer control. In this comprehensive review, we explore the dynamic crosstalk between the PI3K/AKT signaling pathway, tumor initiation, and circRNAs. We delve into the intricate mechanisms through which circRNAs modulate cancer progression, invasion, and metastasis, shedding light on their multifaceted roles in shaping the cancer landscape. Furthermore, we discuss the potential of circRNAs as promising therapeutic targets and diagnostic biomarkers for cancer management. By elucidating the complex interplay between PI3K/AKT signaling, tumor biology, and circRNAs, we pave the way for the development of innovative therapeutic strategies in cancer treatment. This review underscores the importance of unraveling the intricate molecular networks governing cancer pathogenesis. By elucidating the involvement of the PI3K/AKT pathway and its intricate interplay with circRNAs, we contribute to a deeper understanding of the molecular underpinnings of cancer. Ultimately, this knowledge can guide the development of novel therapeutic interventions and diagnostic approaches for improved cancer management. As we gain a more comprehensive understanding of the complex interplay between the PI3K/AKT signaling pathway, tumor initiation, and circRNAs, we unlock the potential to revolutionize cancer treatment and pave the way for more personalized and effective therapeutic strategies.

Keywords: MicroRNAs, Circular RNAs, Pancreatic Cancer, PI3K/AKT Signaling Pathway

1. Introduction

Cancer is a very complex disease with different clinical characteristics and complex etiologies, such as impairment of DNA, all types of RNAs and proteins, and other factors [1-3]. As cancer is very important to health and quality of life, [4-6] a lot of novel treatments have been suggested [7-8]. Targeted therapy and immunotherapy are relatively new therapies that improve the overal survival of patients with cancer [9-10]. For example, circular RNAs (circRNAs) control tumor development and progression. CircRNA is a

novel, stable, non-coding RNA with a covalently closed structure in eukaryotes and viruses originating from pre-mRNA via back-splicing [11-14]. Based on various studies, circRNAs are considered important agents in many diseases, although the mechanism of their function is relatively unknown [15]. One of the circRNA mechanisms involved in cancer progression is its action as a competitive endogenous RNAs (ceRNA) or microRNAs (miRNA). For example, tumor suppression Circ101237 upregulates MAPK1 through mir-490-3p sponging in a type of lung cancer [15]. Furthermore, circRNAs can affect cancers by interacting with proteins; for instance, circRNA cIARS binds to RBP ALKBH5, which blocks cell autophagy [16].

Moreover, circRNAs regulate cancer progression via interaction with the phosphoinositide 3-kinase (PI3K)/AKT pathway as a signal transduction regulator and vesicle trafficking; thus, they can act as targets in tumor treatment [17]. Based on previous studies, the PI3K/ AKT pathway does not work correctly in cancer [18-20]; therefore, different functions of cells, such as proliferation and death deregulation [21, 22], lead to cancer progression. Based on this information, investigation of the crosstalk between the PI3K/AKT pathway, tumor initiation, and circRNAs can help clinicians and patients to experiment more successfully.

2. The Role of PI3K/AKT Signal Transduction Pathway in Cancer

Phosphoinositide 3-kinase (PI3K) is one of the members of the lipid kinase family [23], which consists of three types, class I–III, [17, 24, 25]. Class I PI3Ks are more important in cancer. PI3K has two main domains; the catalytic (p110) and the regulatory (p85) domain [26, 27]. One of PI3K's activation ways is PI3K interaction with connexin or growth factor receptors (GFR) holding phosphorylated tyrosine residues, and subsequently, causes a modification in dimers conformation. Furthermore, it also can be stimulated through Ras binding to p110 [28-30].

Many growth factors and signaling agents, like G-protein associated receptors, fibroblast growth factor (FGF), B-cell receptors (BCR), as well as vascular endothelial growth factor (VEGF), can promote receptor tyrosine kinases (RTKs) which leads to PI3K autophosphorylation [31-35]. In some cases, the autophosphorylation occurs through docking sites provided by the p85 subunit, whereas in other cases, it occurs through adapter proteins, such as the insulin receptor which promotes PI3K through insulin receptor substrate-1 (IRS-1) [35, 36]. At last, phosphorylated PI3K converts PIP2 to PIP3, which induces PDK1 and AKT [37, 38]. Subsequently, AKT regulates the downstream signaling agents: p21, TGFβ, p27, ataxin-1, Bad, GABA receptors, NF-κB, and mTOR. PI3K can also regulate other signaling pathways via BTK, PDK1, and Rac molecules [39].

AKT has been introduced as a serine/threonine kinase containing a core kinase and a C-terminal domain that can bind to mTOR complex 2 (mTORC2). According to different investigations, phosphorylated AKT (p-AKT) induces cell proliferation, angiogenesis, invasion, and metastasis, whereas blocks apoptosis [40]. Furthermore, mTOR usually overexpresses various cancers [41]. The PI3K/AKT/mTOR pathway works as an essential mediator in monitoring nutrient, energy, as well as stress levels. mTORC1 can activate 4E-binding protein 1 (4EBP1) and p70S6 kinase 1 (S6K1) as downstream translation factors which express cancer-associated genes [41]. This deregulation can occur either by the genes' mutation or amplification of the PI3K pathway, loss of PTEN (phosphatase and tensin homolog deleted on chromosome 10) tumor suppressor as a PI3K pathway blocker, or RTKs over-activation which leads to tumor progression and metastasis [42]. The catalytic subunit of the PI3Kα isoform is PIK3CA which is usually mutated in human breast, ovarian, and lung cancers [43]. E542K and E545K mutations in the active site of the p110 subunit are hotspots that change the conformation of PI3Kα, leading to its exposure to the membrane and finally its activation [44]. The H1047R mutation in the kinase domain mimics Ras activity, which leads to the PI3K membrane localization. Another reason is a mutation of PTEN, frequently in the phosphatase domain, which defects its tumor suppressor activity. Moreover, the AKT mutation elevates its activity in tumors. The E17K mutation in the PH domain increases the AKT ability in binding to PIP3, causing AKT phosphorylation. Furthermore, EGFR is an upstream regulator of this pathway which is usually mutated or up-regulated in cancers. In-frame deletions as well as missense mutations in EGFR auto-activate downstream agents in the PI3K pathway [45]. Therefore, the PI3K/AKT signaling pathway plays a very important role in tumor induction, so the study of its mechanisms of action will provide us with some valuable information for tumor treatment.

3. The PI3K/AKT/mTOR Signaling Transduction in Cancer Progression

AKT/mTOR is introduced as important regulator of cell proliferation. mTOR inhibitors including chemical agents like rapamycin or nutrient starvation lead to G1 arrest. mTOR downstream agents such as 4E-BP1 and P70S6K induces the G1 phase via the control of G1 cyclins (D- and E-type cyclins) transcription or the sequestration of cyclin-dependent kinase inhibitor 1 (p21CIP1/WAF1) in the cytoplasm as well as cyclin-dependent kinase inhibitor 1B (p27Kip1), which inactivate cyclin kinase inhibitors. Moreover, mTOR increases the cyclin D1 binding to a cyclin-dependent kinase (CDK) for cell cycle stimulation. Cyclin D1 up-regulation causes the G1 transition to the S phase. mTOR also controls the biosynthesis of nucleotides, proteins, and lipids which are required for cell division [46]. So, prevention of the PI3K/AKT/mTOR signal transduction can limit tumor proliferation (Figure 1).

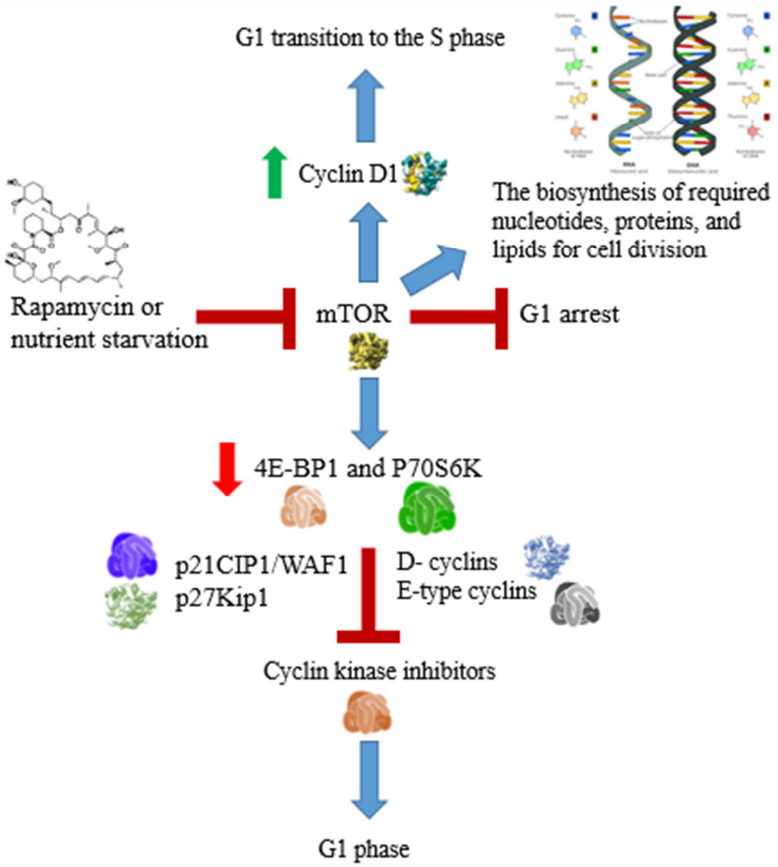

Figure 1. *The role of mTOR in cancer progression. mTOR is adjusting cell cycle trough downstream molecules.*

4. The PI3K/AKT/mTOR Signal Transduction in Tumor Metastasis

When tumor cells dissociate from the original tissue, invade, and migrate to distant sites, metastasis occurs. The PI3K/AKT/mTOR pathway plays a role in the metastasis process through the RTKs, cytokines, or hormone stimulation. AKT phosphorylates mTORC1 and its targets like p70S6K (Thr 389) and 4EBP1 (Thr 37/46). Activation of 4EBP1 up-regulates transcription factors like Slug, Snail, and Twist [47] which increases mesenchymal markers such as vimentin and N-cadherin but down-regulates epithelial markers such as ZO-1, E-cadherin, and claudin. The PI3K/AKT/mTOR pathway controls migration and invasion through F-actin reorganizing. AKT can also activate an actin-associated protein, palladin, via Ser507 phosphorylation to control migration [48]. The PI3K/AKT/mTOR axis can activate p70S6K as an upstream regulator of Cdc42 and Rac1 in control of actin reorganization during metastasis. p70S6K also over-expresses and increases the activity of matrix metalloproteinases (MMPs) as a proteolytic enzymes for the degradation of extracellular matrix (ECM) during the invasion. For example, p70S6K up-regulates MMP-9 and induces its function in ovarian cancer [45]. So, based on mentioned investigations, as the PI3K/AKT/mTOR pathway is very important in migration, invasion, and metastasis, the prohibition of key molecules in this pathway is a potential approach for tumor therapy.

5. The PI3K/AKT/mTOR Signal Transduction in Survival and Chemoresistance

The PI3K/AKT/mTOR activity causes chemotherapeutic and apoptosis resistance in a lot of cancers through factors such as the Bcl-2 family, X-linked inhibitor of apoptosis protein (XIAP), mouse double minute 2 homolog (MDM-2), and Forkhead box O3 (FOXO3a) transcription factor [49]. In the case of apoptosis, the Bcl-2 family is the main factor in tumor multidrug resistance and survival. Bcl-2 proteins release cytochrome C from the mitochondrial membrane by changing its permeability, which causes caspase-induced death. Up-regulation of the AKT pathway components unbalances Bcl-2 proteins. AKT phosphorylates BAD (Bcl-2-associated death) at Ser112 or Ser136, blocks hetero-dimerization of pro-survival agents like Bcl-2 and Bcl-xL, and finally prohibits apoptosis. AKT also regulates XIAP. Activated XIAP binds to caspase and blokes its function; so, the apoptosis is blocked. Furthermore, AKT phosphorylates and stabilizes XIAP at the Ser87 which prohibits cisplatin-mediated induced cell death [50]. AKT also phosphorylates MDM-2 at Ser166 and Ser186, an inhibitor of p53. As p53 activates pro-apoptotic BAX, when it degrades, the balance

between pro-survival and pro-apoptotic proteins will disturb. P53 loss leads to resistance to chemotherapeutic-mediated apoptosis. The FOXO3 induces apoptosis via the Bcl-2 up-regulation or death receptor ligands like tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and Fas ligand. FOXO3 phosphorylation and transportation occur out of the nucleus via AKT. Furthermore, AKT overexpression down-regulates FOXO3 [45]. Regarding mentioned investigations, the PI3K/AKT/mTOR blockage decreases the survival and chemotherapeutic resistance of cells.

6. PI3K/AKT/mTOR Signal Transduction in Tumor Angiogenesis

Angiogenesis is the creation of blood vessels which is a common tumor hallmark, essential for tumor progression and metastasis. Because it supplies oxygen and nutrients for fast growth and repels extra components [51]. Angiogenesis is controlled by the PI3K/AKT/mTOR pathway through the regulation of the hypoxia-inducible factor-1α (HIF-1α) mRNA and protein which start tumor angiogenesis. When environment oxygen is normal, prolyl hydroxylase domain proteins (PHDs) ubiquitinate HIF-1α via hydroxylation but under hypoxic conditions, PHD blockage stabilizes HIF-1α, so, HIF-1α protein accumulates, contributes to a complex with HIF-1β, and finally, stimulates the hypoxia response element (HRE) transcription factor, which expresses pro-angiogenic proteins like MMPs, VEGF, angiopoietin-1/2, as well as nitric oxide synthase (NOS). HIF-1α at a high level induces MMP transcription, which is essential for the degradation of ECM and connective tissue barriers as well as angiogenic agents to reach endothelial cells. Moreover, HIF-1α up-regulates VEGF which elevates endothelial cell growth. The over-activated AKT changes the endothelial nitric oxide synthase (eNOS) distribution which causes nitric oxide (NO) accumulation, as well as the formation and the blood vessels remodeling. Therefore, the AKT/mTOR/p70S6K blockage attenuates angiogenesis, which is a potent tumor treatment [45].

7. The PI3K/AKT Pathway in the Tumor Multidrug Resistance

Chemotherapy has decreased the mortality of cancer patients, but the 5-year survival does not increase sigmificantly, mainly because of intrinsic or acquired chemoresistance [52]. Multidrug resistance (MDR) introduces resistance to administered as well as non-administered drugs with various structures and mechanisms of action [53]. Many mechanisms generate MDR like apoptosis destruction through the over or under-expression of related agents. For example, a cell cycle alteration can lead to cancer cell proliferation and drug resistance [54]. Furthermore, the over-activation of efflux pumps like adenosine triphosphate (ATP)-binding cassettes (ABC) transport the anticancer drugs across the cell membrane [55]. A special metabolism in cancer cells is rapid aerobic glycolysis to produce ATP from consuming glucose and induces drug efflux [56, 57].

3'-phosphorylated phosphoinositides activate the PI3K/AKT pathway that plays an important role in MDR in numerous cancers, including breast cancer, ovarian cancer, leukemia, melanoma, lung cancer, and hepatocellular carcinoma [58-60]. A minimum of one change in PI3K occurs in a variety of tumors [61]. The MDR usually activates the PI3K/AKT pathway, which leads to longer-term survival of cancer cells, drug resistance, and cancer stem cell (CSC) characteristics. However, most of the time, the activated PI3K/AKT pathway is not the only cause of MDR, and the deregulation of other agents has a synergistic effect. For example, this pathway synergizes a lot of the targets regulating cell growth, apoptosis, and cellular metabolism that are related to MDR. Survival signals protect tumor cells from death and are not the same as apoptosis resistance, and both of them are essential MDR regulators in chemotherapy [62]. For instance, Bcl-2 proteins and X-linked apoptosis proteins (XIAP) regulate a lot of cell life and death signals in the mitochondria, where the ultimate cell fate is determined. More resistant cells synthesize more Bcl-2 and/or XIAP19 proteins. As an abnormal activity of the PI3K/AKT pathway increases anti-apoptotic genes like Bcl-2 and XIAP, whereas decreases apoptotic genes like Bax to regulate MDR, it counteracts the chemotherapeutic-induced apoptosis [63].

Based on Hu et al. study, the MDR breast tumor was associated with an abnormal PI3K/AKT/NF-κB pathway [64]. The inducible activity of PI3K/AKT/NF-κB in some tumor cells like pancreatic cancer is tightly associated with tumorigenesis and lead to apoptosis as well as MDR-like cell proliferation [65].

Moreover, P13K/AKT/mTOR can underlie MDR in cancer cells via micro-RNA (miRNA) deregulation. miRNAs can affect this pathway by blocking target genes' transcription with various roles in behavior as well as tumorigenesis [66]. In general, these lead to mutations in key agents of the P13K/AKT/mTOR pathway such as PTEN, PIK3CA, and AKT, which ultimately cause MDR. Yue et al. discovered that mir-182 up-regulation decreased the Herceptin resistance in Herceptin-resistant cells, relatively because of the PI3K/AKT/mTOR inactivation. PI3K/AKT/mTOR is a necessary way to MDR through the change of oncomirs in malignant cells. Along with these findings, long non-coding RNAs affect chemoresistance [67].

The PI3K/AKT/mTOR pathway is complicated because it alters continiously, and numerous various agents that induce MDR can affect it. PI3K/AKT increases cancer proliferation through GSK-3β phosphorylation as a subtype of GSK-3 (a serine/threonine kinase) which changes proliferation in response to different stimuli [68). GSK3β Dysfunction leads to cancer cell proliferation, and it is up-regulated in certain cancer types such as ovarian, colon, liver, as well as pancreatic cancers [69]. Although GSK-3β plays key role many type of pathways, it is mainly considered an important factor in the PI3K/AKT pathway, especially a potent

downstream product of the AKT gene in the chemotherapy escaping which lead to MDR. Because AKT inactivates GSK-3β via phosphorylation [70]. GSK-3β is activated through phosphorylation of S9 and its other residues, which can be inactivated by proteasomal degradation. In consequence, AKT increases, so it phosphorylates GSK-3β at S9 and subsequently inactivates it again [69]. AKT activity decreases E-cadherin expression as β-catenin also has some interactions with cell membrane E-cadherin, the loss of E-cadherin elevates the cytoplasmic β-catenin, which can be removed by the GSK-3β very fast. On the other hand, when GSK-3β is inactive and phosphorylated, cytoplasmic β-catenin accumulates and enters the nucleus, where it can interact with different cytokines like lymphokine activating factors [67]. The over-expression of c-Myc, cyclinD1, and c-Jun can induce tumor proliferation and over-express the target genes like survivin and MDR1, which subsequently will cause MDR [70].

8. The circRNA/PI3K/AKT Axis in Tumor

The exact role of circRNAs in the regulation of physiological processes is unknown yet [15]. However, some evidence shows the significant role of circRNAs in different diseases such as cancer. One of the usual circRNA mechanisms is its activity as ceRNAs of tumorigenic miRNAs. For example, Circ101237 stimulates the MAPK1 expression in NSCLC to inhibit tumor progression through miR-490-3p [71] (Figure 2). Moreover, CircRNA controls cancer initiation and progression via interaction with proteins. For example, cIARS blocks autophagy through interaction with RBP ALKBH5 [16].

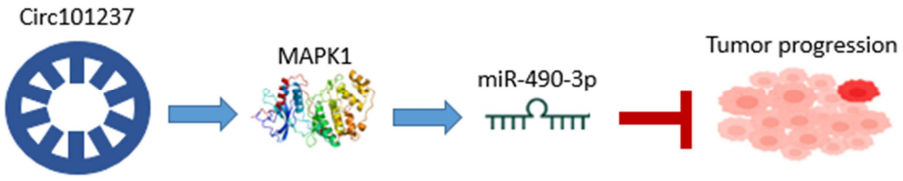

Figure 2. *Circ101237 stimulates the MAPK1 expression in NSCLC to inhibit tumor progression through miR-490-3p.*

The discovery of circRNA increased our knowledge about cancer initiation, progression, and treatment [72]. CircRNAs are not enough for cancer progression, just like signaling pathways or agents. CircRNAs control cancer progression and metastasis via interaction with the PI3K/AKT pathway [73, 74]. CircRNAs control cell functions as well as the occurrence and development of cancer through the PI3K/AKT pathway. circRNAs affect PI3K/AKT signaling pathway via ceRNA, which activates or represses related pathways through miRNA sponging. Investigation on the structure and function of circRNAs as well as the circRNA/PI3K/AKT axis has been performed very recently [67].

9. Association of microRNA and the PI3K/AKT Pathway in Pancreatic Cancer

Pancreatic cancer (PCa) is a major cause of cancer-related mortality worldwide. Numerous agents and signaling pathways are associated with this chronic disease. PI3K/AKT is one of the downstream signaling pathways of KRAS signaling which leads to apoptosis inhibition and cell proliferation. PTEN is an important target of mir-221, mir-21, and mir-181a [24-26]. Decreased expression of mir-221 inhibits the proliferation and migration of Panc-1 and MiaPaCa-2 cells. mir-21 blocks apoptosis, cell cycle arrest, and sensitivity to gemcitabine [24]. Enforced expression of mir-181a increases the migration of PCa cell migration [26]. Whereas mir-200c and mir-375 act as tumor suppressors of the PI3K/AKT pathway. mir-200c expression in pancreatic ductal adenocarcinoma (PDAC) has a relationship to EMT [75] and MUC4 [76]. MUC4 is considered a HER2 stabilizer and induces AKT, which activates downstream agents, such as N-cadherin [77, 78]. Overexpression of mir-200c causes significant downregulation of MUC4 mRNA and protein levels. PDK1 is another downstream kinase of PI3K, and its mRNA is a direct target of mir-375 in PDACs [27, 79]. mir-375 blocks PDAC cells via the AKT pathway more than via the MAPK pathway [67]. One of the key miRNAs in PCa progression is mir-451a, which is sponged by Circ0001085 via PI3K/AKT pathway regulation [80].

In PCa, circNOLC1 is overexpressed, whereas circITCH is clearly under expressed [81, 82]. The up-regulation of CircMBOAT2 in PCa is associated with poor prognosis [80]. Furthermore, circMBOAT2 levels were positively associated with the Gleason score and pathological T stage. Functionally, circMBOAT2, circNOLC1, and circITCH upregulation control several cellular processes such as proliferation, invasion, migration, and metastasis through the circRNA/PI3K/AKT axis in this cancer [80-82]. Circ0001085 can induce EMT in PCa in vitro [83]. CircMBOAT2 induces tumors and metastasis in PCa cells in vivo [20].

Moreover, in PCa, circNFIB1 is strongly under-expressed, whereas circBFAR and circEIF6 are up-regulated [84-86]. Increased levels of circNFIB1 lead to lymphatic metastasis in pancreatic cancer [85]. circBFAR upregulation predicts a high TNM stage and, in conclusion, a poor prognosis [84]. In addition, circEIF6 expression induces cell proliferation, migration, invasion, and metastasis while blocking apoptosis

in PCa cells. These findings were obtained by siRNA-related knockdown experiments [85]. circNFIB1 inhibits VEGF-C and weakens LNM through mir-486-5p sponging and PI3K/AKT blocking in PDAC [85]. In addition, CircEIF6 controls cell functions through mir-557 over-expression, SLC7A11 under-expression, and deactivation of the PI3K/AKT pathway in PCa [86]. CircBFAR stimulates MET via mir-34b-5p sponging and overexpression of the MET/PI3K/AKT axis in PDAC [84]. Based on in vivo studies, decreased circBFAR or circEIF6 may lead to lower weights and volumes of PDAC tumors [17, 67].

10. Conclusions and Future Perspectives

CircRNAs are appropriate markers for the diagnosis, prognosis, and treatment of various cancers. In this regard, the most important finding is that circRNAs may act via molecular relationships with the agents of classic pathways of signal transduction, such as the PI3K/AKT pathway, which is closely related to tumor development and pathogenesis. They can control cell death and proliferation, and play an important role in cell processes such as migration, invasion, and angiogenesis. The circRNA/PI3K/AKT axis has attracted increasing attention because of its therapeutic potential and regulatory role in the biological functions of cells. There is a long way to understand the underlying mechanisms of nc-RNAs. For example, the networks of these RNAs and different older pathways, such as Wnt, P53, NF-kB, and NF-κB.

Contributions

Zahra Taheri and Mahsa M. Amoli planned the study and looked into and revised the paper; Zahra Taheri, Nafise Noroozi and Mahsa M. Amoli taken part in unique draft arrangement; Zahra Taheri collected the references and offer assistance with checking on the paper; all authors have examined and affirmed the article.

Conflict of Interest

The authors declare that they have no competing interests.

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