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Review Article

Modulation of cancer progression by circRNA/ NF-kB axis

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ABSTRACT

The newest class of noncoding RNAs with distinctive characteristics is called circular RNAs (circRNAs). These novel RNAs are more stable than other RNAs because they lack 5' and 3' ends, instead having their two ends created from pre-mRNA through a process called back-splicing. They are also widely expressed in a variety of species, including viruses, plants, and mammals. There is growing evidence that circRNAs are enriched in the NF-κB pathway. The development of many types of malignancies is associated with aberrant activation of the NF-κB pathway. Recent findings indicate that the circRNA/NF-κB axis controls the expression of genes linked to cancer and, consequently, the growth of tumors. Moreover, circRNAs might interact with the NF-κB pathway to affect biological processes of cells. A comprehensive understanding of the molecular processes behind the involvement of circRNA linked to the NF-κB pathway in the progression of distinct malignancies would provide novel opportunities for cancer therapy. Therefore, this article will briefly discuss the function of circRNAs and the NF-κB pathway in cancer. Next, it will address the crucial role that circRNAs associated with NF-κB play in the progression of different types of malignancies.

Keywords: Circular RNA, Cancer, NF-κB pathway, Back-splicing

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Introduction

Cancer is currently regarded as the leading cause of death and a severe public health concern worldwide, with an anticipated 1,958,310 newly diagnosed cases and 609,820 deaths in the United States in 2023 according to GLOBOCAN 2023(1, 2). Because of its complex etiology, which involves changes in both genetic and epigenetic characteristics, cancer is complex in both its clinical features and variability (3). According to the reports, female breast cancer has surpassed lung cancer to become the most commonly diagnosed disease (4). Cancer advances as malignant cells migrate to nearby locations, increasing tumor heterogeneity and facilitating cancer cell invasion and dissemination (5). Ample evidence has demonstrated that alterations in cell signaling pathways, especially nuclear factor-κB (NF-κB), give cancer cells different characteristics and malignant potentials (6-8). Information for cancer diagnosis and targeted therapy may be derived from molecular alterations in cancer-related genes and associated signaling pathways. Emerging data has revealed that different cancers have a robust correlation

with epigenetic mechanisms. Epigenetic alterations are implicated in changing chromatin structure and performance through several mechanisms comprising histone modifications, DNA methylation, and non-coding RNA (ncRNA) interferences, which are the key epigenetic changes studied so far (9, 10).

In terms of length, ncRNAs are categorized into two categories: microRNAs with a length < 200 nucleotides and long ncRNAs (lncRNAs) with a length > 200 nucleotides(11-13). A novel class of long non-coding RNAs, called circular RNAs (circRNAs), is implicated in several physiological and pathological processes(14, 15), most notably the advancement of cancer(16). These newly formed ncRNAs are single-stranded, covalently closed molecules that are created from pre-mRNA by a process known as back splicing. CircRNAs have a distinct shape that makes them more stable than linear RNAs. As a result, they may be employed as biomarkers for the detection, assessment, and management of cancer(17). The evidence supporting the potential role of circRNAs in cancer biology has grown in recent years. They act to control the behavioral phenotypes of tumors, including proliferation, migration, and invasion via numerous mechanisms involving microRNA sponging, transcriptional regulation, and protein interaction(18, 19). Although the regulatory function of circRNAs in physiological processes is still unclear, a common circRNA-mediated mechanism that circRNAs operate as competitive endogenous RNAs (ceRNAs) of microRNAs (miRNAs) in tumorigenesis has been suggested(20). On the other hand, they can alter signaling pathways and differently enable or inhibit signal transmission to downstream effectors thanks to their multigene regulation capabilities(21-23).

Nuclear factor-kappa B (NF-κB), a pro-inflammatory transcription factor, is a master regulator and a significant transcription factor that controls inflammation, immunological responses, and the development of cancer(24, 25). Several studies have shown that some types of cancer have abnormal activation of the NF-kB signaling pathway(26, 27). It has been recently demonstrated that circRNAs interact with the NF-κB pathway throughout the cancer process to control a number of biological processes within cells(28-30). These linkages imply a possible crosstalk between circRNAs and the NF-κB pathway in cancer growth, which may find application as pharmacological therapeutic targets and as potential biomarkers for tumor diagnosis. Thus, in the current review, this article will focus on the role of circRNAs, which directly target the NF-κB pathway in human malignancy, and play a critical role in tumorigenesis and tumor progression.

The NF-kB pathway in tumorigenesis

NF-κB functions as a transcription factor that is found in the cytoplasm of a cell, influencing the production of growth and immunity genes. RelA (p65), Rel B, c-Rel, NF-κB1 (p50/p105), and NF-κB2 (p52/p100) are the five master transcription factors that make up NF-κB. This pathway can be activated by a variety of stimuli, including growth factors, reactive oxygen species (ROS), bacterial and viral products (dsRNA and lipopolysaccharide), cytokines, UV and ionizing radiation, and growth factors (31). These five genes can generate seven proteins with sequence similarity in terms of having a Rel Homology Domain (RHD), which in turn play a vital role in DNA binding, dimerization and interaction with inhibitors(32). NF-κB activation can be suppressed by the "inhibitor of KB" (IκB) proteins; the most crucial ones to be engaged in this process are IκBα, IκBβ, and IκBγ. IKKα and β are kinases, whereas γ is the complex's regulatory element (33). Once dimerized, NF-κB can attach itself to the enhancer or promoter of target genes, acting as a co-repressor or co-activator (34). Transcription activation domains (TADs) are also found in RelA, c-Rel, and RelB proteins, however TADs are absent from p50 and p52 proteins, which only cause transcription repression(35). When the cells are at rest, NF-κB dimers are trapped in the cytoplasm by combining the inhibitory protein IκB (IκBα/β/γ). However, when the cells are stimulated, NF-κB translocates into the nuclear and quickly activates, attaching to κB sites to elevate gene expression(36).

Generally, there are two primary routes for NF-κB activation: canonical (classical) and non-canonical (alternative). Tumor necrosis factor-α (TNF-α), interleukin (IL)-1, viral proteins, lipopolysaccharide (LPS), physical and chemical stress, and other pro-inflammatory cytokines serve as stimuli in the canonical pathway. The first step in the canonical pathway of NF-κB signaling is the stimulation of Transforming growth factor-beta (TGF-β)-activated kinase 1 (TAK1). This leads to the activation of a trimeric IκB kinase (IKK) complex, which consists of regulatory and catalytic subunits. When the IKK complex phosphorylates IκB at a serine residue, NF-κB, especially the p50/65 heterodimer, translocates to the nucleus and initiates NF-κB signaling. IKKs may also efficiently regulate the activity of substrates other than IκB, such as p53, and other molecular adaptors like Rap1 and helicases like DEAD-box decapping enzyme 20 (DDX20). Furthermore, phosphatases such as wild-type p53-induced phosphatase 1 (Wip1) possess the ability to dephosphorylate phosphorylated IKK substrates. As a result, Wip1 functions as a significant negative regulator of this signaling network by suppressing NF-κB signaling. NF-κB can bind to the κB site of several genes involved in immune response, inflammation, and other processes in the nucleus(37-39). Numerous receptors, including the lymphotoxin-β receptor (LTβR), CD40, B-cell activating factor belonging to TNF family receptor (BAFFR), and receptor activator for NF-κB (RANK), can activate the non-canonical

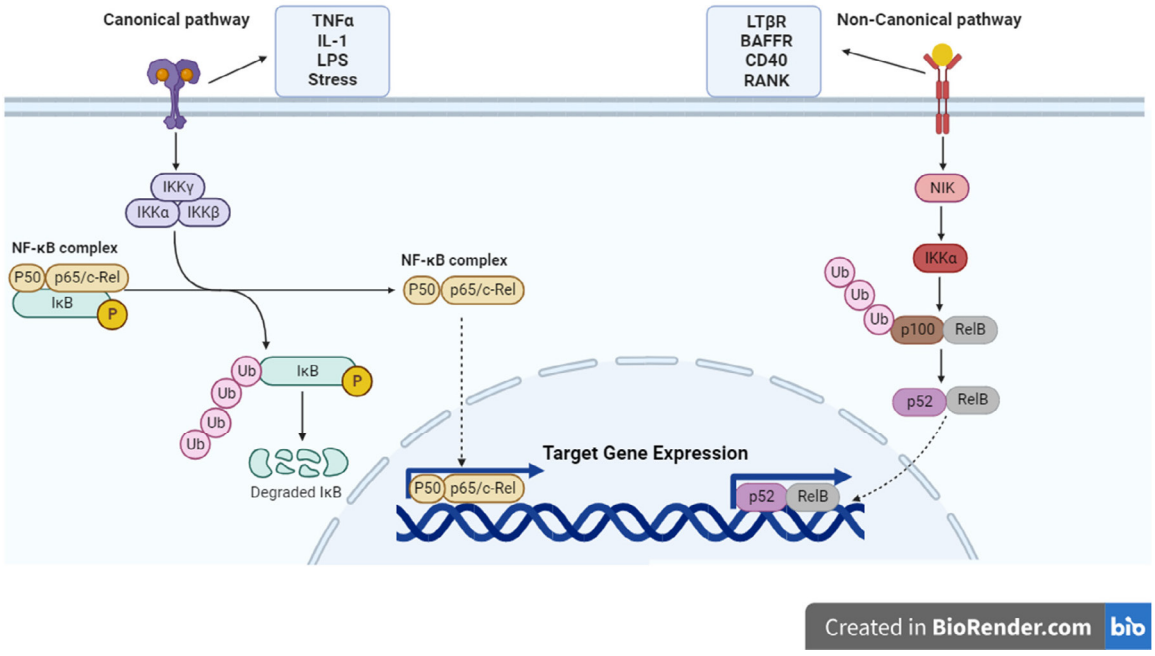

Figure 1: A schematic representation of NF-κB signaling. The canonical NF-κB pathway (left) induced by lipopolysaccharide (LPS), tumor necrosis factor-α, interleukin-1 (IL-1), and stresses. The noncanonical pathway (right) induced by different factors.

pathway. NF-κB-inducing kinase (NIK) phosphorylates and stimulates IKKα in this pathway. Subsequently, IKKα phosphorylates p100 at the carboxy terminal serine residue, causing it to be degraded by proteases and converted into p52, which then leads the p52/RelB complex to translocate to the nucleus. Ultimately, the p52/RelB complex binds to the κB site of many genes crucial in the survival, differentiation, and maturation of cells (40, 41) (Figure 1).

For cells to operate, NF-κB signaling must be strictly controlled, and dysregulation of these well-planned processes has been observed in cancer. According to reports, NF-κB plays a critical role in the tumorigenesis process (42, 43). Stimulation of the NF-κB signaling pathway can encourage angiogenesis, proliferation, and migration, three characteristics of tumor cells that are important for the development of cancer (44). Moreover, the growth and survival of cancer cells are positively correlated with inflammation. Inflammation is brought on by NF-κB activation, and this can accelerate the growth of cancer. Furthermore, the pro-tumorigenic microenvironment is directly influenced by the increased NF-κB activity in tumorous tissue (45, 46). Ultimately, this microenvironment could result in immunological suppression and encourage tumor escape from immunosurveillance. Apart from influencing the growth, invasion, and angiogenesis of cancer cells, NF-κB has a close relationship with cancer stem cells and the epithelial-mesenchymal transition (EMT) process, all of which are recognized to affect the spread of cancer (47, 48). Strong evidence suggests that other mechanisms, such as circRNAs, can also control NF-κB. Numerous data indicate that circRNAs regulate the course of cancer via activating the NF-κB pathway (49, 50); this will be covered in more detail later.

Overview on the role of circRNAs in cancer

CircRNAs, a novel class of endogenous covalently closed RNA molecules, were first discovered in RNA viruses at the end of the 20th century. They are generally synthesized during the back-splicing process from pre-mRNA, in which the 3′ splice donor sequence is joined to the downstream 5′ splice acceptor sequence (14). They are divided into six subtypes: I) exonic-circRNA; II) intronic circRNA, which is produced from single or multiple exon and intron, respectively; III) exonic-intronic circRNAs, which comprise both exon and intron; IV) antisense-circRNAs, which are derived from the same gene locus as their linear RNA isomer but are instead transcribed from the opposite strand; V) intergenic-circRNAs, which are generated from parent genes located outside known gene loci; and VI) tRNA intronic-circRNAs, which are derived from splicing pre-tRNA intron (51). CircRNAs can function by regulating target gene expression, linear RNA transcription, and protein generation. Besides, numerous studies have confirmed that the function of circRNAs is various including acting as miR decoys or sponges, interaction with protein (RNA binding proteins [RBP]), regulation of alternative splicing, gene transcription, protein translation, and epigenetic (52). Studies have begun to highlight that circRNAs dysregulation are involved in various diseases such as cardiovascular disease (53),

neurodegenerative diseases (54), metabolic disorders (55), and cancers (52). Accumulating data proposed that circRNAs regulate cancer progression by alternating the expression of miRNA targets. For instance, CircSEPT9 increased breast cancer progression by sponging miRNA-637 to activate STAT3 protein (56). Additionally, circRNAs modulate the development of cancer by directly changing the transcription of related genes or interaction with RBPs. For example, because circZKSCAN1 targets the RBP fragile X mental retardation protein, it attenuates the stemness of hepatocellular carcinoma cells (57). Interestingly, certain circRNAs that have both the internal ribosome entry site (IRES) and the AUG start codon are able to regulate translational gene expression. This effect on cancer has not been completely understood yet, though (58).

Breast cancer

Breast cancer is thought to be the most common cancer among women globally (59). Breast cancer is a diverse disease with fluctuating prognosis and clinical features (60). Breast cancer is influenced by a number of variables, most of which are related to modifications in the expression of certain genes, including those that encode non-coding RNAs (61). Recent findings have demonstrated that many circRNAs, mostly through miRNA sponging, were functionally engaged in the development of breast cancer (62). However, a fuller knowledge of this axis (circRNAs/ NF-κB) in breast cancer is considered a hot subject in the area of cancer due to its significance in the progression of breast cancer and the interaction between circRNAs and this key signaling pathway (63). In this way, it was found that the circABCC4 was overexpressed in tumor tissues relative to normal tissues. By up-regulating miR-154-5p and blocking the NF-κB pathway, CircABCC4 knockdown suppressed the viability, migration, and invasion of breast cancer cells (64). Furthermore, circ-TPGS2 expression increased breast cancer cell dissemination by activating NF-kB signaling through sponging miR-7 to inhibit the level of tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6) (65). As an oncogenic gene, circIKBKB is upregulated in bone-metastatic breast cancer tissues. Its overexpression also redacted the formation of the p65/IκBα complex, sustained the nuclear accumulation of NF-κB induced by TNF-α, and increased the amount of NF-κB bound to DNA. Additionally, it has been shown that circIKBKB interacted competitively with the N-terminal of NF-κB with IκBα. Meanwhile, eukaryotic translation initiation factor 4A3 (EIF4A3), a pre-mRNA splicing factor, directly bound to the circIKBKB flanking region to promote circIKBKB cyclization (66). On the other hand, circRNA 000911 functions as a miRNA sponge for miR-449a, which in turn enhances the function of the NF-κB signaling pathway, hence playing an anti-oncogenic role in breast cancer cells (67). Similarly, Hu and colleagues demonstrated that circRNA-0001283 was low-expressed in breast cancer tissues and its overexpression increased apoptosis and inhibited invasion and proliferation of breast cancer cells. In addition, they declared that this circRNA might control NF-kB pathway via miR-187/ HIPK3 axis (68). Moreover, it has been revealed that circRNF10, as a tumor suppressor, regulated breast cancer progression by interacting with RBP. Mechanistically, this circRNA by interaction with DEAH (Asp-Glu-Ala-His) box helicase 15 (DHX15) blocked DHX15-NF-κB p65 positive feedback loop, thereby suppressing breast cancer progression (69). Similar to circRNF10, hsa_circ_0043278 functions as a tumor suppressor gene, inhibits breast cancer progression by sponging miR-455-3p, increasing the level of EI24, reducing the activity of NF-κB pathway (70). Considering the role of RBPs in the biosynthesis of circRNA, a recent study indicated that tumor exosomal SERPINE2-derived hsa_circ_0001103 (cSERPINE2) was shuttled to tumor associated macrophages and remarkably increased MALT1, a vital regulator of immune responses, elevated the levels of IL-6 via stimulating NF-κB signaling, leading to promoting proliferation and invasion of breast cancer cells (71) (Figure 2).

Esophageal cancer

Globally, esophageal cancer has a high incidence rate and fatality rate, and esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) are two main histological subtypes of this cancer. EAC is widespread in western nations like North America and Western Europe; however, ESCC is the primary histologic type of esophageal cancer in Eastern Asia and Africa (72). Studies on the impact of circRNAs on the progression of ESCC are few. To the best of our knowledge, three documents investigated the effects of circRNA on esophageal cancer through the NF-kB pathway. First, Huang and co-workers reported that ciRS-7 plays a critical role in the migration and invasion of ESCC cells via regulation of miR-7/ marker Kruppel-like factor-4 (KLF-4) and activation of NF-κB pathway. Mechanistically, the expression of KLF-4, as the target of miR7, elevated in ciRS-7 transfected ESCC cells, as well as, knockdown of KLF-4 reduced overexpression of ciRS-7. Furthermore, ciRS-7 boosted IKK-α phosphorylation, which in turn raised p65 expression (73). Second, it has been demonstrated that overexpression of circCYP24A1 led to activation NF-κB pathway by binding to M2 isoform of pyruvate kinase (PKM2), which enhanced the secretion of chemokine (C-Cmotif) ligand 5 (CCL5) and increase malignant progression of ESCC (74). Third, hsa_circ_0021727 acts as a ceRNA to activate the TAK1 binding protein 1 (TAB1) /NF-κB pathway by sponging miR-23b-5p

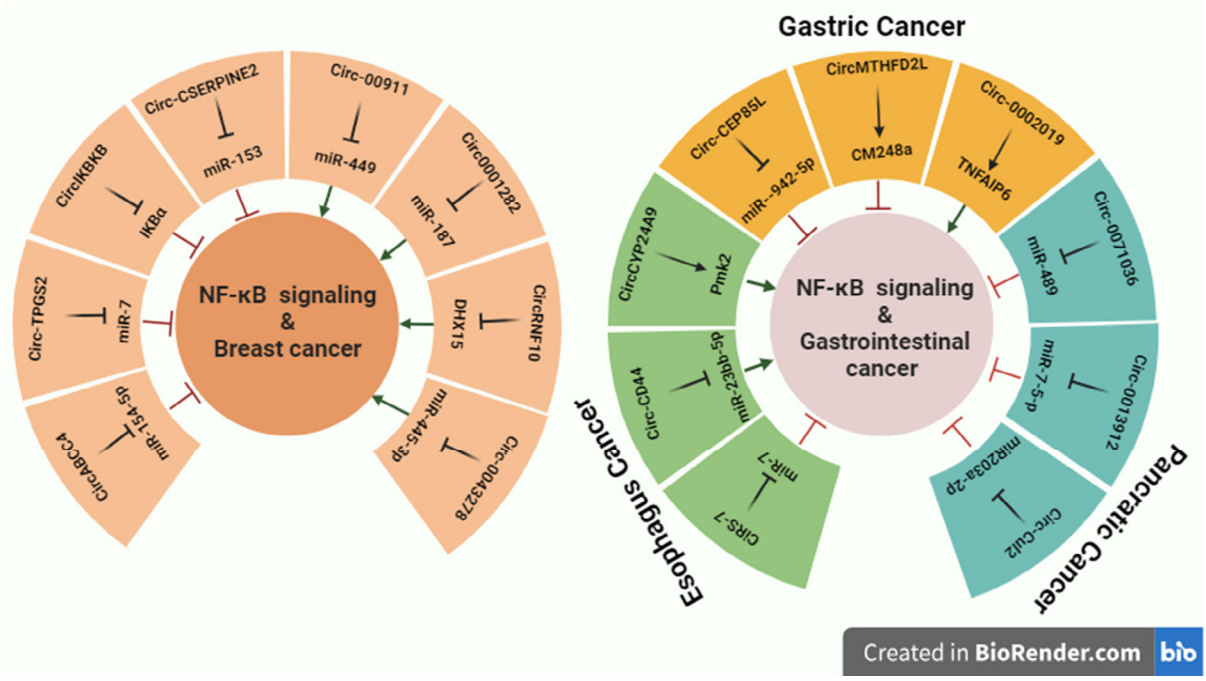

Figure 2: Regulation of NF-κB signaling by circRNAs in breast, gastric, esophageal, and pancreatic cancers.

in ESCC progression (75) (Figure 2). Putting these data together, it seems plausible that these circRNAs implicated in ESCC development by serving as miRNA sponges or inhibitors to prevent the interactions between these miRNAs and their targets in NF-κB pathway. As a result, even though circRNAs' gene expression patterns have been shown to alter significantly during the development of ESCC, their function as ceRNAs in this cancer is still only partially understood and requires further research.

Gastric cancer

Gastric cancer is known as the fifth most diagnosed malignancy and the fourth most prevalent cause of cancer mortality globally (4). Increasing evidence has indicated the role of dysregulated circRNAs in the progression of GC via different pathways, especially the NF-κB signaling pathway. Circ-CEP85L enhanced NFKBIA (also known as IKBA, NFKBIAIA) expression, as a member of the family of NF-κB inhibitors, by functioning as a sponge of miR-942-5p; thereby, suppressing proliferation and invasion of gastric cancer (76). Furthermore, Circ_0002019, as an oncogenic circRNA, was overexpressed in gastric cancer tissues and cells. This circRNA increased the progression of gastric cancer via stimulation of the NF-κB pathway by enhancing TNFAIP6 mRNA stability by polypyrimidine bundle-binding protein 1 (PTBP1), as an important protein in the modulation of pre-mRNA splicing (77). Interestingly, CM-248aa was encoded by circMTHFD2L, which was identified as a downregulated circRNA with coding potential in gastric cancer. CM-248aa interrupted the SET-PP2A interaction through binding to the acidic domain of SET in the nucleus, which rescued PP2A activity and negatively regulated the NF-kB signaling pathway. Collectively, CM-248aa, which is encoded by circular MTHFD2L RNA, repressed the progression of gastric cancer by targeting the SET-PP2A interaction (78) (Figure 2).

Pancreatic cancer

Pancreatic cancer is a cancer of the digestive system that has a short prognosis and few available therapeutic options. The most frequent primary cancer of the pancreas is called pancreatic ductal adenocarcinoma (79). Since pancreatic cancer is difficult to diagnose early, most patients with the disease have a delayed diagnosis; as a result, pancreatic cancer has the lowest 5-year relative survival rate (9%) of all cancer types (80). Several studies have demonstrated how circRNAs function as oncogenes or tumor suppressors in pancreatic cancer by influencing proliferation, migration, invasion, and metastasis through a variety of pathways, such as miRNA sponge activity and cancer-related signaling pathway regulation, such as the NF-κB pathway (81-84). Circ_0013912 was found to be upregulated in pancreatic ductal adenocarcinoma tumor tissues and cells, according to Guo et al. Its knockdown resulted in the suppression of pancreatic ductal adenocarcinoma cell growth, migration, and invasion by sponging miR-7-5p, one of the microRNAs that regulates the NF-κB pathway (85). In a different investigation conducted by Han and

colleagues, it was demonstrated that hsa_circ_0071036 activation is an important modulator of PDAC carcinogenesis by sponging miR-489, which functions as a strong metastasis inhibitor and acts downstream of KRAS/NF-kB signaling to reduce its tumor suppressive effect (86). Moreover, in inflammatory cancer-associated fibroblast, circCUL2 was overexpressed. As a ceRNA, this circRNA regulated the miR-203a-3p/MyD88/NF-κb/IL6 axis, causing normal fibroblasts to change into inflammatory cancer-associated fibroblasts. This, in turn, increased the activation of the STAT3 signaling pathway in pancreatic cancer cells, speeding up the progression of pancreatic ductal adenocarcinoma (84) (Figure 2).

Hepatocellular carcinoma

The most prevalent kind of primary liver cancer, hepatocellular carcinoma, is linked to a high number of cancer-related deaths. Hepatocellular carcinoma incidence and progression have been discovered to be closely correlated with a set of circRNAs linked to the circRNA/NF-κB axis (87). HCC migration and metastasis were regulated by CircRNA-101368 through microRNA-200a, high-mobility group box 1 protein (HMGB1), receptor for advanced glycation end products (RAGE), and NF-kB signaling downstream (88). On the other hand, by blocking the NF-kB signaling pathway, circ5379-6 prevents HCC from metastasizing (89). Tu et al. observed that after knocking down ZEB1, ERG1, NF-KB, correspondingly, circ-0003006 was considerably downregulated in the ZEB1 knockdown HCC cells, while the circ-0003006 expression has no difference in the ERG1, NF-KB knockdown group (90). A study that examined the impact of circRNAs in cancer treatment resistance revealed that circZFR enhanced cisplatin (DDP)-resistant HCC cell lines. Also, CAFs-derived exosomes improved chemoresistance by increasing the expression of circZFR in HCC cells via STAT3/ NF-κB pathway (91) (Figure 3). Therefore, given that circRNAs may play a crucial role in the development of hepatocellular carcinoma, they may be valuable as biomarkers for the management, identification, and therapy of this malignancy. This section discussed the roles played by circRNA in the development of hepatocellular carcinoma, with an emphasis on how they specifically affect the NF-κB pathway and might therefore be targets for therapeutic intervention.

Colorectal cancer

Colorectal cancer, the second most deadly and third most common cancer, is estimated to cause 0.9 million deaths and 1.9 million incident cases worldwide in 2020 (92-94). In recent years, there is rising data that indicated a crosstalk between lncRNAs notably, circRNAs with colorectal cancer-related pathways (95-97). Because CircGLIS2 is an oncogenic circRNA, it abnormally activates the NF-κB signaling pathway through the miR-671 sponge mechanism, thereby being involved in the progression of colorectal cancer (98). It has been shown that circPLCE1 encoded circPLCE1-411 to enhance the ubiquitin-dependent degradation of the critical NF-κB regulator RPS3 via directly binding the HSP90α/RPS3 complex, thereby promoting the dissociation of RPS3 from the complex and reducing NF-κB nuclear translocation, thus promoting colorectal cancer proliferation and metastasis both in vitro and in vivo. RPS3 is a crucial modulator of NF-κB, and HSP90α is regarded as a partner of RPS3 that controls its degradation reliant on ubiquitin (99). In sum, future researches are necessary to study the actual mechanism of the circRNA/ NF-κB axis in the development of colorectal cancer and to utilize them as a biomarker or target for treatment of this cancer (Figure 3).

Lung cancer

One of the main causes of cancer-related mortality globally is considered to be lung cancer; it is categorized into two types: small-cell lung cancer and non-small-cell lung cancer (NSCLC), with NSCLC constituting the vast majority of lung cancer cases (100). Finding possibly targetable circRNAs early in the course of cancer development may have substantial therapeutic implications (101, 102). For a considerable amount of time, there has been evidence to support the theory that circRNAs involved in NF-κB pathway regulation were important for the progression and development of lung cancers. For instance, Ma et al. reported that circ_0020123 increased NSCLC cell progression by regulating the miR-384/TRIM44 axis. Respecting the role of TRIM44 in the increment of cell growth by regulating the NF-κB pathway in NSCLC, it can be said that circ_0020123 exerts its effects on the progression of NSCLC via the NF-κB pathway indirectly (103). Furthermore, it was elucidated that ciRS-7 regulates proliferation, migration, invasion, and apoptosis of NSCLC cells via the NF-kB pathway by sponging miR-7 (104). In more recent years, a study illustrated that Circ_cMras, as a tumor suppressor gene, repressed lung adenocarcinoma progression using the NF-κB pathway via modulating alpha-beta hydrolase domain 5 (ABHD5)/ adipose triglyceride lipase (ATGL) axis (105) (Figure 3). It seems that further researches are required to be done, to find the exact molecular mechanisms underlying the circRNA related ceRNA function in the progression of lung cancers.

Glioma

Glioma is the most frequent and deadly primary nervous system tumor, defined by a variety of genetic molecular abnormalities. Astrocytomas, oligodendrogliomas, and ependymomas are several

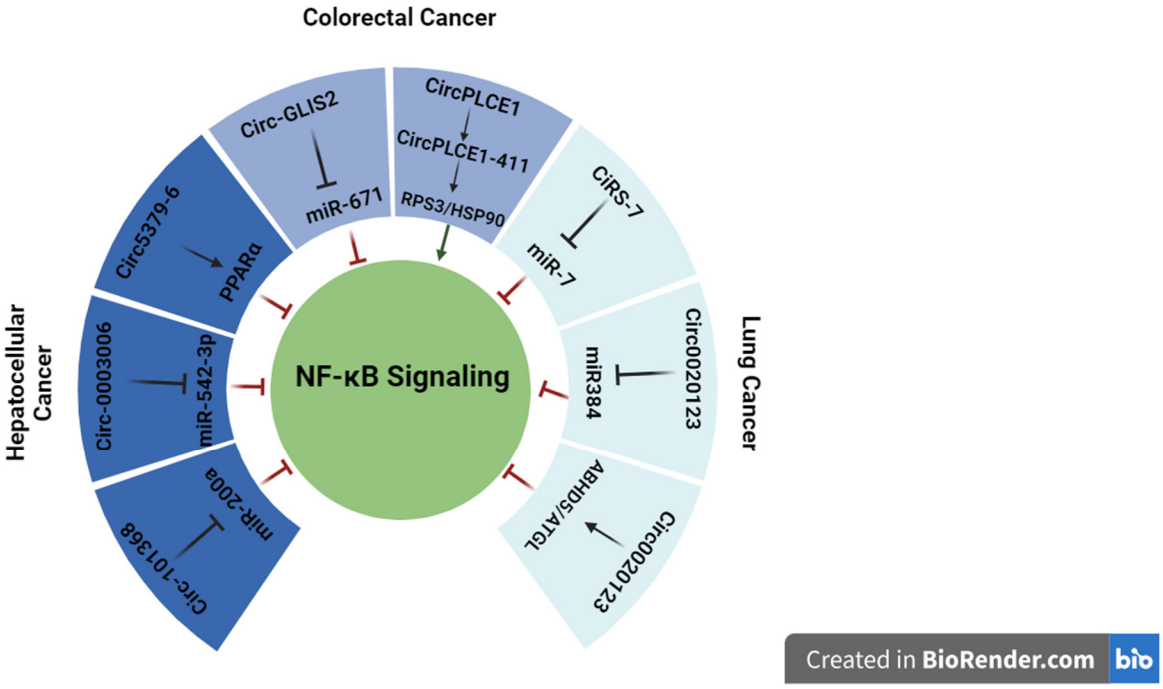

Figure 3: Regulation of NF-κB signaling by circRNAs in lung, hepatocellular, and colorectal cancers.

types of gliomas that may be identified based on the histologic subtype and grade of malignancy (106). Numerous investigations have shown that the abnormal expression of circRNAs and their interaction with signaling pathways in gliomas may provide a unique molecular target for glioma therapy (107-109). For example, in gliomas, hsa_circ_0008225 acts as a tumor suppressor by sponging miR-890 and subsequently enhancing Zinc Finger MYND-Type Containing 11 (ZMYND11) activity (110). In addition, Liang et al. reported that five circRNAs (hsa_circ_0072389, hsa_circ_0072386, hsa_circ_0008621, hsa_circ_0072387, and hsa_circ_0072391) act as a ceRNA to activate the NF-κB pathway to promote glioma via miR-338-5p/I kappa B kinase interacting protein (IKBIP) (111). CircKPNB1 was overexpressed in glioma and linked to enhanced glioma stem cell proliferation, neurosphere formation, and stemness. In more detail, DiGeorge Critical Region 8 (DGCR8), circKPNB1, and Spi-1 proto-oncogene (SPI1) are all part of a positive feedback loop. CircKPNB1 has the capacity to control SPI1's nuclear translocation and protein stability. DGCR8 can bind to and stabilize circKPNB1 when it is transcriptionally upregulated by SPI1. In glioma stem cells, this positive feedback loop can activate NF-κB signaling and constantly upregulate TNFα expression and release (112) (Figure 4).

Prostate cancer

Prostate cancer is currently the first and second leading cause of new diagnosis and mortality, accounting for 21% of all new cancer cases and 10% of all death cases in men (113). There are few documents about the interplay between circRNAs with signaling pathways in prostate cancer. According to the performed study by Guo et al., circARHGEF28 inhibits the progression of prostate cancer via repressing the miR-671-5p/LGALS3BP/NF-κB axis. To be more precise, this circRNA sponged miR-671-5p to increase lectin galactoside-binding soluble 3 binding protein (LGALS3BP). This, in turn, inactivated the NF-κB pathway, ultimately halting the development of prostate cancer (114). Furthermore, prostate cancer cells and tissues exhibited overexpression of circNOLC1, which is upregulated by NF-κB. This promotes the progression of prostate cancer through the miR-647/progestin and adipoQ receptor family member 4 (PAQR4) axis (115) (Figure 4).

Other cancers

Ovarian cancer and cervical cancer are the two most common gynecological malignancies (116). In cervical cancer, circRNA NFATC3 functions as a miR-9-5p sponge and controls the SDC2/NF-kB signaling pathway (117). In addition, it was demonstrated that the upregulation of hsa-circ-0009910 was associated with an unfavorable prognosis of ovarian cancer due to NF-κB activation through miR-145 down-regulation (118).

Bladder cancer continues to be the most frequent urinary tract cancer and one of the most common

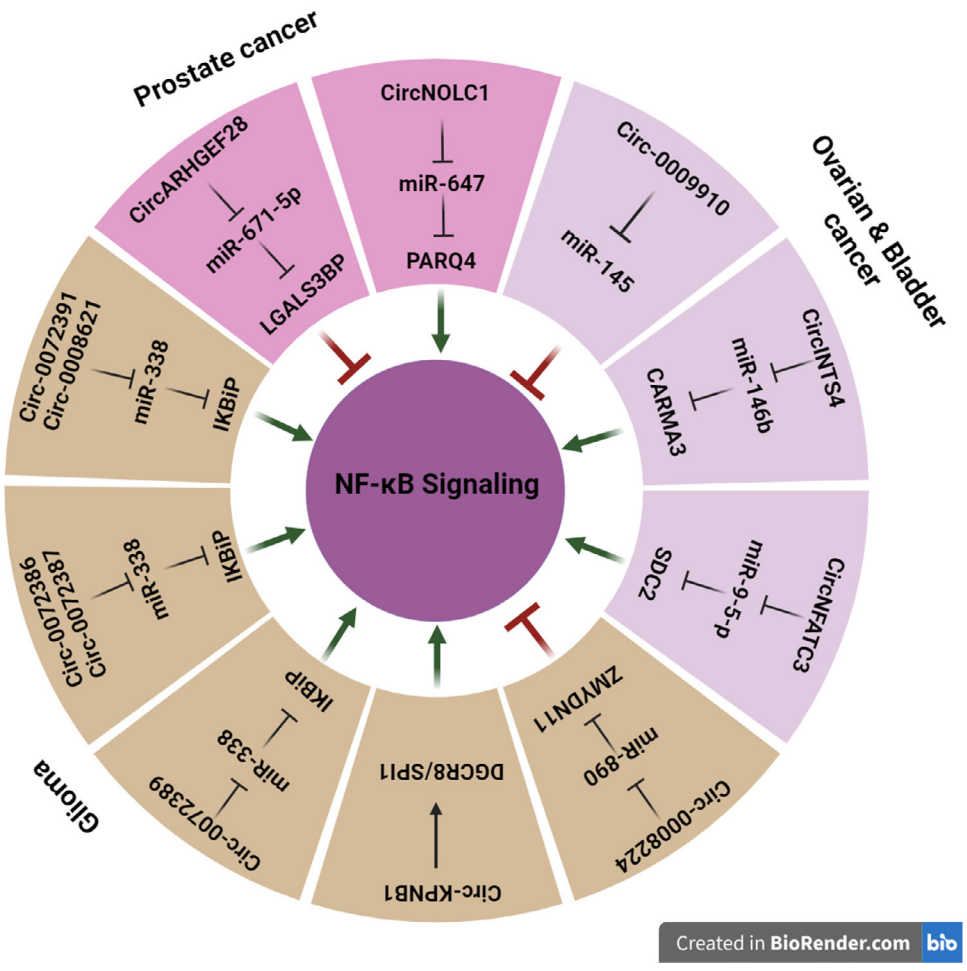

Figure 4: Regulation of NF-κB signaling by circRNAs in glioma, prostate, bladder and ovarian cancers.

malignancies globally (119, 120). Zhang and colleagues revealed that circINTS4 was overexpressed, while miR-146b was low expressed in bladder cancer tissues and cell lines relative to normal tissues. Mechanistically, in bladder cancer cells, circINTS4 stimulated the NF-kB signaling pathway in a CARMA3-mediated manner by directly binding to miR-146b and inhibiting its ability to target CARMA3 (121) (Figure 4).

Conclusion

CircRNAs are key players in a variety of cellular signaling pathways that are engaged in a wide range of cellular processes. Dysregulation of these non-coding RNAs is implicated in a variety of human diseases, including cancer. CircRNAs that are dysregulated impact several cellular signaling pathways, including NF-κB signaling, as well as pathways linked to inflammation, cell death, proliferation, and other processes that contribute to the development of cancer. Research revealed that circRNAs' control over the NF-κB pathway played a major role in the development of tumors and that this control may be helpful in the treatment of cancers. Moreover, it has been discovered that circRNAs may be targeted to stop the carcinogenesis process. Furthermore, additional investigations will provide more details regarding the role of circRNAs in the regulation of other signaling pathways in malignancies, and fresh clinical study will open up new therapeutic avenues.

Conflict of Interest

The authors have nothing to declare.

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