Discover Oncology

https://doi.org/10.1007/s12672-026-04875-8

Article in Press

Crosstalk between circRNAs and the MAPK signaling pathway in cancer progression

Received: 12 August 2025

Accepted: 16 March 2026

Published online: 07 April 2026

Cite this article as: Zahedi M., Maghrebi-Ghojogh E., Ahangari F. *et al.* Crosstalk between circRNAs and the MAPK signaling pathway in cancer progression. *Discov Onc* (2026). https://doi.org/10.1007/s12672-026-04875-8

Mohammad Zahedi, Ehsan Maghrebi-Ghojogh, Fatemeh Ahangari, Maryam Zamani Sani, Alireza Mafi, Kiavash Hushmandi, Seyed Ali Olianasab, Salman Daneshi, Mina Alimohammadi, Seyedeh Mahdieh Khoshnazar, Najma Farahani, Mehrdad Hashemi & Afshin Taheriazam

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

ARTICLE IN PRESS

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

ARTICLE IN PRESS

Crosstalk between circRNAs and the MAPK signaling pathway in cancer progression

Mohammad Zahedi[1], Ehsan Maghrebi-Ghojogh[2], Fatemeh Ahangari[3], Maryam Zamani Sani[4], Alireza Mafi[5], Kiavash Hushmandi[6], Seyed Ali Olianasab[7], Salman Daneshi[8], Mina Alimohammadi[9]*, Seyedeh Mahdieh Khoshnazar[10]*, Najma Farahani[11*], Mehrdad Hashemi[11,12]*, Afshin Taheriazam[11,13]*

1. *Metabolomics and Genomics Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*
2. Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
3. *Department of Immunology, Pasteur Institute of Iran, Tehran, Iran*
4. *Department of Clinical Biochemistry and Laboratory Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
5. *Department of Genetics and Biochemistry, School of Medicine, Arak University of Medical Sciences, Arak, Iran*
6. *Department of Epidemiology, University of Tehran, Tehran, Iran*
7. *Department of Plant Science, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran*
8. *Department of Public Health, School of Health, Jiroft University of Medical Sciences, Jiroft, Iran*
9. *Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
10. *Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran*
11. *Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital, TMs.C., Islamic Azad University, Tehran, Iran*
12. *Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran*
13. *Department of Orthopedics, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran*

***Corresponding authors:**

Mina Alimohammadi, mina.alimohammadi11@gmail.com

Seyedeh Mahdieh Khoshnazar, m_khoshnazar@kmu.ac.ir

Najma Farahani, Najmafarahani@gmail.com

ARTICLE IN PRESS

ARTICLE IN PRESS

Afshin Taheriazam ‖ a.taheriazam@iautmu.ac.ir

Mehrdad Hashemi‖ mhashemi@iautmu.ac.ir

Abstract

Noncoding RNAs (ncRNAs), including long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and small ncRNAs, play critical roles in regulating biological processes and disease development. Among these, circRNAs, characterized by their single-stranded, covalently closed structures, act as protein templates, microRNA sponges, and transcriptional regulators, exhibiting high stability and distinct expression profiles. CircRNAs play an important role in several diseases, including autoimmune disorders, cardiovascular diseases, neurological conditions, and cancers. In cancer, they influence key mechanisms like cell cycle development, angiogenesis, apoptosis, proliferation, motility, and metastasis. Meanwhile, the mitogen-activated protein kinase (MAPK) signaling pathways—especially the Ras/Raf/MEK/ERK cascade—are central to controlling cell survival, proliferation, and tumor development, with hyperactivation of ERK linked to cancer progression. Despite the important roles of both circRNAs and MAPK pathways in oncogenesis, the mechanisms underlying their interplay remain poorly understood. This review aims to fill this knowledge gap by examining the bidirectional interactions between circRNAs and MAPK signaling in cancer and explores therapeutic implications, focusing on strategies such as circRNA modulation (targeting their functions as transcriptional regulators

ARTICLE IN PRESS

or microRNA sponges) and MAPK pathway inhibition to control cancer progression.

Keywords: Cancer progression; CircRNAs; MAPK signaling pathway; diagnostic biomarkers; Therapeutics targets

1. Introduction

Noncoding RNAs (ncRNAs) represent a substantial portion of the transcriptome and play key biological roles in several cellular processes (1). Long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and small ncRNAs are among the increasing number of unique ncRNAs discovered thanks to recent advancements in sequencing techniques and data analysis (2). Single-stranded, covalently closed RNA molecules known as circRNAs are found in many species. CircRNAs perform biological functions as protein templates and microRNA (miR) sponges. Additionally, intronic circRNAs (ciRNAs) and exon–intron circRNAs (ElciRNAs) act as transcriptional regulators (3-5). CircRNAs exhibit a longer half-life and greater resistance to RNase R compared to linear RNAs (6), which makes them suitable candidates for both therapeutic targets and diagnostic biomarkers. Several studies have shown their unique expression signatures and critical biological functions in a range

ARTICLE IN PRESS

of illnesses, including autoimmune disease (7), cardiovascular disease (8), neurological disorders (9), and cancer (10-12).

CircRNAs are well acknowledged to play key roles in cell cycle progression, angiogenesis, and apoptosis, as well as in cell proliferation, motility, and metastasis (5). CircRNAs may be crucial modulators of long-term proliferative signaling and the development of cancer (13). Circ-FOXO3 is one of the examples. By forming a ternary complex with CDK2 and p21, the tumor suppressor circ-Foxo3 prevents the cancer cell cycle from progressing (14). Another example of strong carcinogenic activity is the interaction between circ-Amotl1 and c-myc. Circ-Amotl1 can up-regulate c-myc targets, enhance c-myc stability, and improve the retention of nuclear c-myc (15). One well-known example of a circRNA that may be translated into a protein is Circ-ZNF609 (16). As an oncogene, circ-ZNF609 overexpression results in enhanced tumor development, whereas knockdown results in the opposite effects in mouse xenograft models (17).

ARTICLE IN PRESS

Mitogen-activated protein kinase (MAPK) cascades are important signaling pathways that control several cellular functions, such as stress responses, apoptosis, differentiation, and proliferation. The tumor cell survival depends heavily on the Ras/Raf/MAPK (MEK)/ERK pathway, the most significant signaling cascade among the MAPK signal transduction pathways. The formation and progression of cancer are significantly influenced by the hyperactivation of ERKs (18).

ARTICLE IN PRESS

Even though circRNAs and the MAPK signaling pathway play critical roles in cancer, their interplay remains one of the least studied areas. Despite significant advances in understanding the individual roles of circRNAs and MAPK signaling in cancer progression, the mechanisms by which they interact and contribute collectively to tumorigenesis are still poorly understood. This gap highlights the need to study how they interact, which could lead to the discovery of new cancer therapies. Thus, in this study, we reviewed the bidirectional interaction between circRNAs and the MAPK pathway resulting in cancer progression. We intend to identify new ways to understand how circRNAs control MAPK signaling and how MAPK activity regulates circRNA functions. This will be achieved by developing new models and strategies.

2. MAPK signaling pathway: molecular activation and role in cancer

Mitogen-activated protein kinase (MAPK) cascades mediate the transduction of extracellular stimuli to diverse cellular outcomes such as proliferation, differentiation, inflammation, and apoptosis. There are three major families of MAPKs in mammalian systems, namely, ERK, JNK, and p38, acting in three-tiered kinase modules (MAPKKK → MAPKK → MAPK).

Figure 1 outlines mitogen-activated protein kinase (MAPK) cascades—ERK, JNK, and p38. Extracellular stimuli such as growth factors, mitogens, stress, and inflammatory cytokines activate upstream receptors (RTKs, GPCRs, integrins). This activation triggers small GTPases (RAS, RAP), followed by

ARTICLE IN PRESS

MAP3Ks, MAP2Ks, and MAPKs. These sequential steps result in outputs like cytokine production, apoptosis, cell migration, proliferation, and differentiation. The figure illustrates how diverse stimuli converge on MAPK cascades to regulate cellular functions involved in stress and inflammation responses (19, 20).

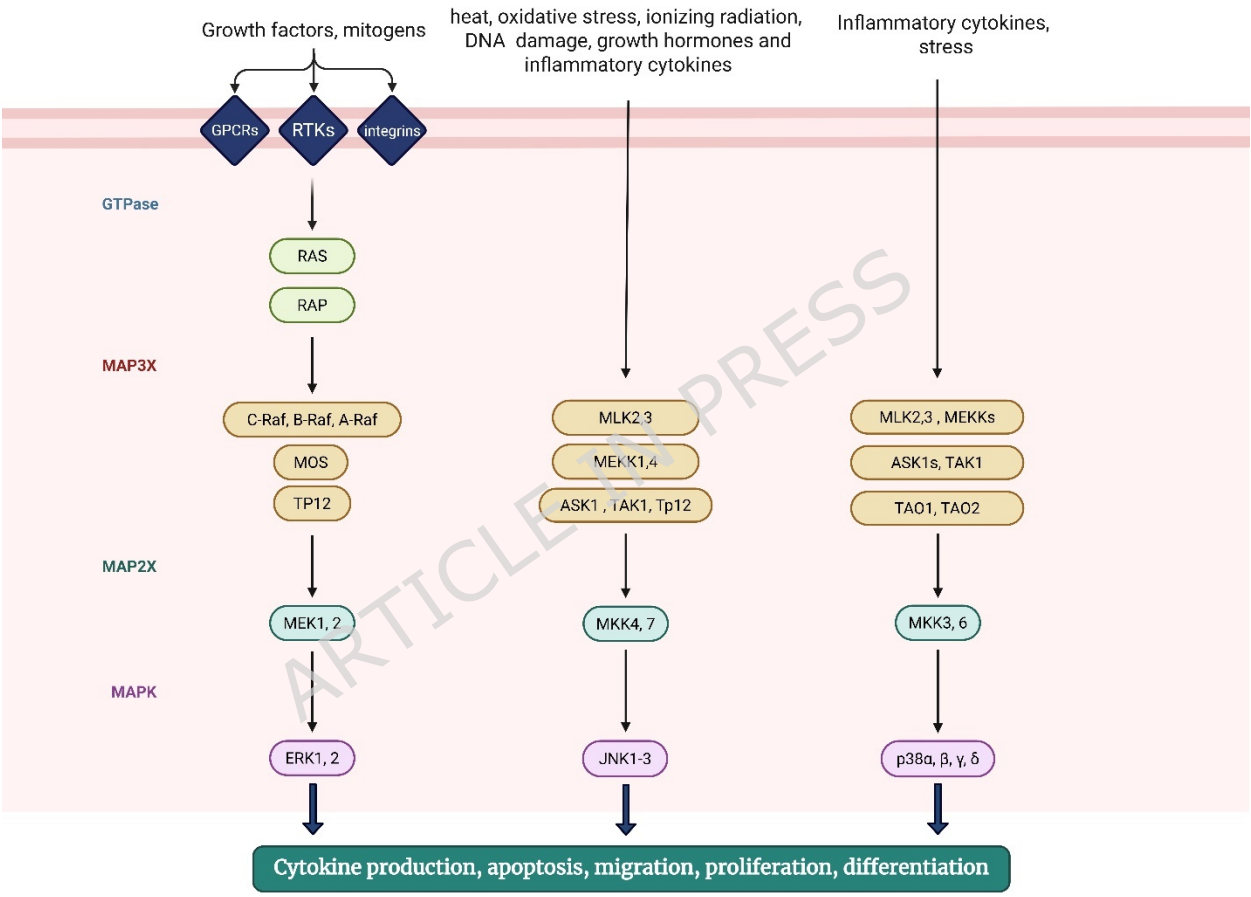


Figure 1. An overview of the MAPK Signaling Pathways and Upstream Stimuli

Protein kinases downstream of cell surface receptors and/or interactions with a small GTPase are the primary routes by which MAPKKK is activated (21).

ARTICLE IN PRESS

First, MAPKKK activates MAPKK by directly phosphorylating it. Then, the activated MAPKK phosphorylates a conserved tripeptide TxY motif at the activation site of MAPK, thereby activating MAPK. When the MAPK is activated, it phosphorylates a variety of substrates in the nucleus and cytoplasm, altering gene expression and protein function to elicit the appropriate biological response (22).

Members of the ERK (extracellular signal-regulated kinase) family (e.g., ERK1/2 and ERK5) are characterized by a conserved TEY (threonine–glutamate–tyrosine) motif located within their activation site, which is essential for their phosphorylation and functional activation. ERK1 and ERK2 predominantly consist of a catalytic kinase domain, whereas ERK5 contains a significantly longer sequence extending from the carboxy-terminal region beyond the kinase domain, suggesting additional regulatory or functional capacities (23-25).

ARTICLE IN PRESS

The ERK1/2 signaling module is important in the cellular response to growth factors and mitogens, primarily mediating processes related to cell proliferation and differentiation. This pathway is activated at the plasma membrane by many cell surface receptors, including receptor tyrosine kinases (RTKs), G-protein-coupled receptors (GPCRs), and integrins. These receptors, upon ligand binding, stimulate downstream signaling through small GTPases, notably RAS and RAP, which serve as molecular switches to relay signals to the MAPK cascade (22). Once activated, RAS and RAP engage upstream kinases in the MAPK cascade, beginning with MAPKKKs such as

ARTICLE IN PRESS

members of the RAF family, as well as MOS and Tpl2. These kinases phosphorylate and activate the MAPKKs, specifically MEK1 and MEK2, in the case of the ERK1/2 pathway. MEK1/2, in turn, phosphorylates ERK1/2 on both threonine and tyrosine residues within the TEY motif, resulting in their full activation. Activated ERK1/2 then translocates into the nucleus to regulate transcription factors and downstream gene expression programs that are essential for mitogenic and differentiative responses (22).

Among the most crucial downstream signaling pathways of MAPKs is the JNK pathway, which is primarily regulated by oxidative stress, UV radiation, inflammatory cytokines (e.g., TNF-α, IL-1β), and DNA damage. A conserved TPY motif in the activation segment of these three JNKs distinguishes them from other members of this family. Upstream kinases such as MEKK1/4, MLK2/3, ASK1, and TAK1 phosphorylate and activate MKK4 and MKK7, which further phosphorylate JNK. Activated JNK translocates to the nucleus, where it phosphorylates central transcription factors c-Jun, ATF2, and Elk-1, thereby regulating the genes that are accountable for apoptosis, inflammation, and cellular stress response (26).

In cancer, JNK signaling is abnormally activated, causing tumor growth and cancer formation by promoting apoptosis resistance and an inflammatory tumor microenvironment. Rho family GTPases Cdc42 and Rac are also involved in the activation of JNK. The GTPases are molecular switches that exist in an inactive GDP-bound state as well as an active GTP-bound state,

ARTICLE IN PRESS

and add additional regulatory complexity to the JNK signaling pathway (22, 27).

One of the strongest downstream effectors of JNK signaling is the AP-1 (Activator Protein-1) transcription factor complex. The complex, consisting of Jun and Fos family proteins, is not only activated in part through c-Jun and family members being phosphorylated by JNK but also mediates gene expression that affects cell growth, differentiation, and apoptosis, and thus cellular response to inflammation and stress (28).

During recent times, several negative regulatory components of the JNK pathway have been identified. Some examples include proteins such as the dual-specificity phosphatase MKP7 that dephosphorylates JNK and certain isoforms of p38 selectively, which suppress JNK signal transduction. Heat shock protein Hsp72 also suppresses JNK activity and therefore controls stress-induced apoptosis. Evi1 oncoprotein also suppresses JNK activation and therefore suppresses stress-induced cell death. These negative regulators serve to counteract activation of the pathway and contribute to the overall tight regulation of JNK signaling (29, 30).

Despite significant advances, there remains much to be elucidated regarding the particular regulation and scaffolding of the JNK pathway. Areas needing research priority are the identification of putative scaffold proteins—CrkII, filamin, β-arrestin-2, JIP2, and JIP3—and upstream MAP3Ks MLK family members, ASK2, MEKK2, MEKK4, and TAK1. Redundancy and context-

ARTICLE IN PRESS

dependent activation of these proteins reflect an elaborate, well-regulated network of signaling (22, 27).

The p38 MAPK pathway represents another large branch of the MAPK signaling pathway. It is primarily activated by environmental and physiological stress stimuli such as ultraviolet (UV) radiation, heat shock, osmotic shock, oxidative stress, and pro-inflammatory cytokines like TNF-α and IL-1β. p38 is phosphorylated and activated by upstream kinases MKK3 and MKK6, which are phosphorylated by MAP3Ks such as ASK1, TAK1, MLK2/3, MEKK1–4, and TAO1/2 (31, 32). The four isoforms of the p38 family are p38α (MAPK14), p38β (MAPK11), p38γ (MAPK12), and p38δ (MAPK13), with distinct expression patterns and substrate preferences. Several downstream targets of phosphorylated p38 include protein kinases MK2/3, MSK1/2, and PRAK, as well as transcription factors ATF2, Elk-1, and p53, which play important roles in regulating inflammation, differentiation, cell cycle arrest, and apoptosis (22).

ARTICLE IN PRESS

Among the p38 MAPK isoforms, p38α is the most abundant and widely studied (33). p38β is downregulated and often shows overlapping functions with p38α. In contrast, p38γ and p38δ display more restricted expression patterns and appear to serve specialized roles (34, 35). Specifically, p38β is enriched in the brain, p38γ in skeletal muscle, and p38δ in kidneys, pancreas, small intestine, and testis (36, 37). Several studies suggest that p38α and p38β cooperate in diverse processes, including sex determination, cardiac development, regulation of mitotic entry, and T-cell activation (38). p38γ and

ARTICLE IN PRESS

p38δ have been implicated in tissue regeneration and immune responses (39). However, there is no genetic evidence indicating that they substitute for p38α functions (40). Interestingly, suppression of p38α can sometimes trigger compensatory activation of p38γ and/or p38δ (41). Overall, the distinct and overlapping contributions of the four isoforms remain to be fully clarified.

Functionally, the p38 MAPK pathway is an important regulator of cellular stress response and immune signaling. Acute p38 activation in normal physiology leads to cell survival and repair, but persistent or inappropriate activation leads to apoptosis, senescence, or tumor suppression. The function of p38, however, in cancer cells also becomes context-dependent, shifting from tumor-suppressive to tumor-promoting depending on tissue type, microenvironment, and signal intensity(42) . For example, chronic activation of p38α has been implicated in chemoresistance, invasion, and angiogenesis in breast and colorectal cancers, while reduced p38 activity in hepatocellular carcinoma (HCC) and melanoma is implicated in uncontrolled cell growth and metastasis. The p38 signaling pathway regulates transcriptional programs and governs cell fate under stress conditions through its interactions with other MAPK branches, such as ERK and JNK. In brief, the double and highly context-dependent functions of p38 MAPK emphasize its complexity in cancer biology. Dissection of the molecular pathways that determine whether p38 acts as a tumor suppressor or tumor promoter can unveil novel therapeutic opportunities, particularly with the targeting of stress (43, 44).

ARTICLE IN PRESS

As previously stated, the dysregulation of the MAPK signaling pathway due to genetic and epigenetic modifications contributes to the development of several human cancers. The primary cause of MAPK signaling hyperactivity and continuous signal transduction which eventually results in tumor progression is mutations in several MAPK signaling pathway components, including upstream membrane receptors such as EGFR, signal transducers such as RAS, and downstream kinases such as BRAF (45).

Increased expression of ERK has been found in a several human tumors, including lung, breast, colon, and ovarian cancer. By activating transcription factors to increase VEGF transcription, ERK/MAPK signaling pathways can raise VEGF expression in tumor cells and encourage the development of blood vessels (18, 46). Moreover, benign cystadenomas and normal ovarian surface epithelium had higher levels of MAPK phosphatase-1 (MKP-1) expression than invasive carcinomas, low malignancy potential tumors, and borderline tumors (47, 48). Moreover, over 40% of cancer cases are caused by overactivation of the conventional MAPK pathway (Ras/RAF/MEK/ERK (MAPK) pathway) (49, 50).

Mutations in upstream regulators such as KRAS, BRAF (in particular the V600E mutation), and EGFR are some of the key drivers of constitutive activation of the MAPK pathway in human cancers. The KRAS mutations (e.g., G12D, G13D, Q61H) lock RAS in an active GTP-bound conformation, resulting in continual stimulation of RAF kinases and persistent phosphorylation of ERK. The BRAF V600E mutation mimics activation loop phosphorylation,

ARTICLE IN PRESS

leading to constitutive MEK/ERK signaling regardless of upstream stimulation. Similarly, EGFR activating mutations (e.g., exon 19 deletions and L858R substitutions) induce downstream RAS–RAF–MEK–ERK activation. These oncogenic mutations not only drive unchecked growth but also serve as therapeutic targets—e.g., BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib, cobimetinib) have shown clinical activity in tumors with MAPK hyperactivation. However, adaptive resistance generally develops by feedback reactivation of ERK signaling or compensatory activation of parallel pathways, highlighting the requirement for combination therapeutic strategies against several MAPK nodes (51). As a result, members of the RAS kinase subfamily are being examined as potential therapeutic targets in the MAPK pathway. One gene family that frequently undergoes mutations in cancer is RAS. KRAS mutations are the most common and are frequently found in colorectal and pancreatic ductal adenocarcinomas. Human cancers are closely linked to BRAF and RAS mutations that dysregulate MAPK signaling (52). The interaction between RAF and RAS is a key event in the activation of MAPK pathways. Active, GTP-bound RAS brings RAF to the plasma membrane, promoting its dimerization and conformational activation. However, RAS binding is not sufficient for total activation of RAF, as other cofactors and post-translational processes (e.g., phosphorylation and release of 14-3-3 protein) are required to lock the kinase's active conformation. Mutations in RAS or RAF disrupting this finely

ARTICLE IN PRESS

ARTICLE IN PRESS

tuned regulation cause constitutive MAPK signaling, which drives oncogenesis and drug resistance in a variety of cancers.

3. CircRNAs : A brief insight into biogenesis and functions

For circRNA biogeneis exon-intron boundary and 3' UTR are essential cis-elements (53). The production of circRNAs primarily occurs through a non-canonical splicing event known as back-splicing mechanisms: (1) lariat-driven circularization (exon skipping), (2) intron pairing-driven circularization, and (3) RNA binding protein (RBP)-driven circularization (54). Other unique groups of circRNAs, including intergenic circRNAs, rt-circRNAs, and f-circRNAs can also be generated by alternative processes and are commonly linked to clinical disorders (55). CircRNAs are classified into three classes based on their composition and cycling mechanisms: circular intronic RNAs (ciRNAs) (4), exon-intron circRNAs (ElciRNAs) (3), and exonic circRNAs (ecircRNAs) (56, 57).

ARTICLE IN PRESS

Numerous circRNAs perform significant biological roles by modulating protein activity, functioning as microRNA or protein inhibitors (also known as "sponges"), or being translated themselves (58). A major mechanism through which circRNAs exert their function is by acting as competing endogenous RNAs (ceRNAs) which means sponging microRNAs (miRNAs) to regulate gene expression (59). For instance, CDR1as, one of the most well-known circRNAs, functions as a miR-7 sponge by containing almost 70 preferentially conserved miR-7 target sites (60, 61). CDR1as increases the expression levels of miR-7-targeting proto-oncogenes (EGFR, CCNE1, and

ARTICLE IN PRESS

PIK3CD) by acting as a miR-7 sponge. In other words, the tumor-inhibitory effects of miR-7 are blocked by overexpression of CDR1as (62). Furthermore, glioma tissues and cell lines have high expression of hsa_circ_0046701, which is able to stimulate cell invasion and proliferation by controlling ITGB8 expression through sponging miR-142-3p (63). Similarly, circGFRA1 acts as a ceRNA in triple-negative breast cancer (TNBC) by sponging miR-34a, thereby modulating the expression of GFRA1. This highlights its potential for TNBC diagnosis and treatment (64). In a parallel fashion, circ-PDE8A serves as a ceRNA for miR-338 in pancreatic ductal adenocarcinoma (PDAC), where it regulates MACC1 and drives tumor invasion via the MACC/MET/ERK or AKT signaling pathways. Therefore, exosomal circ-PDE8A could serve as a valuable diagnostic or prognostic marker for PDAC (65).

Apart from functioning as miRNA sponges, circRNAs can also impact cancer cell behavior by interacting with proteins (59). For instance, circ-Foxo3 interacts with p21 and CDK2 to form a ternary complex that blocks CDK2 activation and thereby inhibits the cell cycle (14). In breast cancer, circ-Amotl1 is found at elevated levels and acts as an oncogene that accelerates cancer progression by binding to c-myc and increasing the expression of c-myc target genes. Indeed, the circ-Amotl1/c-myc complex boosts c-myc's affinity for the promoter sites of genes like HIF-1γ, Cdc25a, ELK-1, and JUN (15).

Modulating transcription is another way that circRNAs can affect cancer cells' activity. As an example, CircSMARCA5 binds to its genomic locus to

ARTICLE IN PRESS

form a circR loop, causing transcriptional pausing and generation of a truncated nonfunctional SMARCA5 protein. This reduces SMARCA5 expression and impairs DNA damage repair, suggesting that targeting circSMARCA5 could sensitize breast cancer cells to cytotoxic drugs (66).

Interestingly, several circRNAs can change cancer cell behavior by encoding peptides. For example, Liu et al. found that circ-EGFR can encode a polymeric novel protein complex, called rolling-translated EGFR (rtEGFR). It co-localizes with EGFR at the plasma membrane and prevents its endocytosis and degradation, thereby sustaining EGFR signaling and promoting glioblastoma progression (67). In addition to the miRNA sponge, transcriptional regulation, interacting with RBPs and translational effects, circRNAs are also involved in alternative splicing (68).

4. The circRNA–MAPK Axis: Mechanistic Interplay

CircRNAs primarily interact with the signaling pathway via different mechanisms, including (1) acting as miRNA sponges to release MAPK-related mRNAs from repression, (2) modulating upstream activators (such as RAS/RAF/MEK), (3) binding directly to signaling proteins to stabilize or scaffold MAPK components, and (4) participating in feedback loops that integrate MAPK signaling with circRNA expression. CircRNAs mainly regulate the MAPK signaling pathway by using the competing endogenous RNA (ceRNA) mechanism. This type of regulation is predominantly achieved through the sponging of microRNAs that target MAPK pathway proteins expression and activity. When a circRNA binds to a miRNA, it prevents the miRNA from binding to its usual target mRNAs (69, 70). For example, recently, it was shown that circ-MAPK4 promotes gliomas by sponging miR-125a-3p, which confirms this circRNA's role in affecting the downstream

ARTICLE IN PRESS

signaling of the MAPK pathway (71). Another example is circ-CEP128, which is a ceRNA for miR-145-5p and decreases its availability. This can affect the MAPK signaling pathway as the inhibition from the miR-145-5p is not present, and can cause the tumor progression related to the MAPK activation (72, 73). The detailed interactions between circRNAs and MAPK signaling will be discussed in the next section.

5. CircRNAs Regulating MAPK Signaling in Cancers

Several cellular processes are regulated by the MAPK signaling pathway, including cell growth, proliferation, differentiation, migration, and apoptosis. Many cancers are thought to develop and progress because of dysregulation of the MAPK pathway (74). The circRNA pathway is also dysregulated in many cancers (75). It has been suggested that circRNAs can serve either as oncogenes or tumor suppressors, depending on their influence on MAPK signaling pathways (**Figure 2**). A study has found that circMAPK1 could target and suppress of MAPK signaling, inhibiting gastric cancer progression and invasion. However, the MAPK pathway-related circRNAs remain under-researched. Several circRNAs, which are involved in cancer development through MAPK and related signaling pathways, are listed in **Table 1**.

ARTICLE IN PRESS

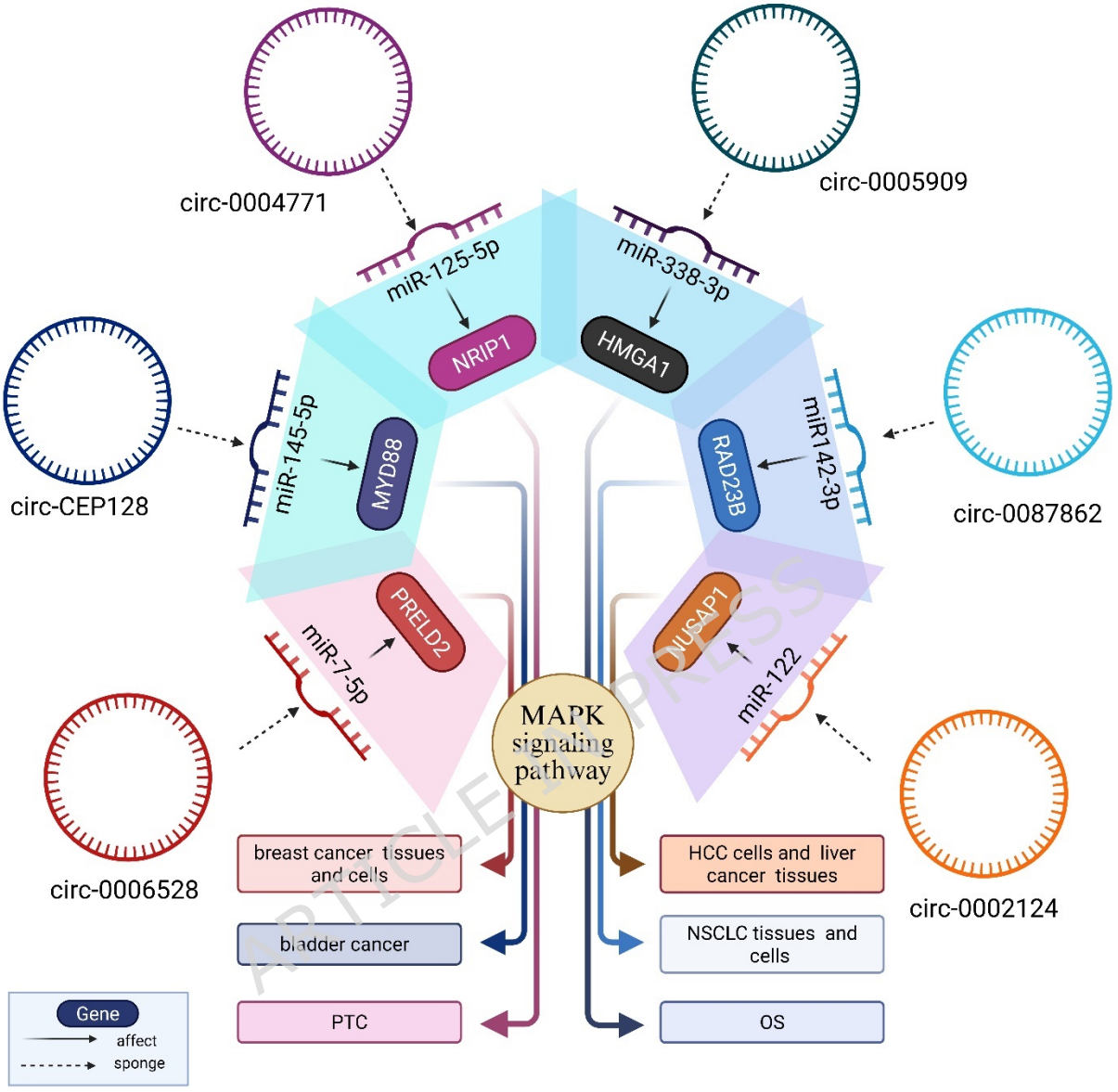


Figure 2. CircRNAs Regulate the MAPK Signaling Pathway through miRNAs in Various Cancer Types.

ARTICLE IN PRESS

Table 1. Several circRNAs implicated in the development of cancer through MAPK and Related Signaling Pathways

CircRNA	Expression	Model/samples	Role	Effect on the signaling pathway	Signaling Pathway/ target	Effect	Potential application	year	Ref
hsa_circRNA_0006528	Upregulated	breast cancer tissues and cells	Oncogene	Activate	MAPK/ERK Raf1	Promote DNA synthesis, cell proliferation, invasion, and migration	Potential therapeutic target	2018	Danfeng Gao (76)
circ-CEP128	Upregulated	bladder cancer tissues and blood	Oncogene	Activate	MAPK miR-145-5p	Promote cell proliferation, invasion, and migration	Potential therapeutic target	2019	Sun (72)
hsa_circRNA_000019 0	Upregulated	NSCLC	Oncogene	Activate	MAPK/ERK	Promote cell proliferation, invasion, and migration	Potential therapeutic target	2022	Ishola (77)
circNRIP1	Upregulated	Renal carcinoma, esophageal SCC, papillary thyroid cancer	Oncogene	Activate	JAK, STAT, MAPK	Promotes cell growth, survival, and malignancy	Potential therapeutic target	2021	Li (78)
hsa_circRNA_0000567	Downregulated	HCC	Tumor suppressor	Inhibit	miR-421/MAPK14	Inhibit proliferation	Potential therapeutic target	2019	Xu (79)
circSLC8A1	Downregulated	Prostate cancer tissues & cell lines (PC-3, DU145)	Tumor suppressor	Inhibit	MAPK, Chemokine signaling pathways, PTEN	Inhibit Migration, invasion, proliferation	Potential therapeutic target	2021	Wang (80)

ARTICLE IN PRESS

hsa_circ_0005909	Upregulated	OS	Oncogene	Activate	miR-338-3p/HMGAI	Promote cell proliferation	Potential therapeutic target	2021	Zhang (81)
hsa_circ_0001313	Downregulated	NSCLC	Tumor suppressor	Inhibit	miR-452/HMGB3/ERK/MAPK	Inhibit cell proliferation	Potential therapeutic target	2020	Zhang (82)
hsa_circ_0006117	Upregulated	PC	Oncogene	Activate	miR-96-5p/KRAS/MAPK	Promote cell proliferation, invasion, and metastasis	Potential therapeutic target	2021	Tao et al. (83)
circTXNDC11	Upregulated	renal cancer tissues and cells	Oncogene	Activate	MAPK/ERK	Promote RCC cells' proliferation and invasion	Potential therapeutic target	2021	YANG (84)
hsa_circ_0003204	Upregulated	cervical cancer tissues and cells	Oncogene	Regulate	MAPK	Promote cervical cancer cell proliferation, migration, and invasion	Potential therapeutic target	2020	HUANG (85)
circUBAP2	Upregulated	prostate cancer cells	Oncogene	Promote	miR-1244/MAP3K2	Promote the proliferation of prostate cancer cells	New therapeutic strategies	2021	LI (86)
circ-RAD23B	Upregulated	NSCLC tissues and cells	Oncogene	Inhibit	miR-142-3p/MAP4K3	Inhibit NSCLC progression	Promising therapeutic target	2022	ZHUANG (87)
hsa_circ_0002124	Upregulated	HCC cells and liver cancer tissues	Oncogene	-	MAPK	Promote HCC cell proliferation	Potential biomarker	2019	FANG (88)

ARTICLE IN PRESS

circFAT1	Upregulated	cervical cancer tissues and cells	Oncogene	Activate	miR-409-3p/CDK8	Promote cervical cancer progression	Promising prognostic biomarker	2021	ZHOU (89)

ARTICLE IN PRESS

ARTICLE IN PRESS

5.1. oncogenic circRNAs

5.1.1. circ_0006528

The PRELID2 gene gives rise to the circular RNA hsa_circ_0006528, also known as circPRELID2, which may contribute to the development of drug resistance in cancer cells. According to previous expression profiling studies, circ_0006528 was among the most significantly upregulated circRNAs in adriamycin-resistant breast cancer cells compared to drug-sensitive tissues. Given its overexpression, it may play a role in the mechanisms that enable cancer cells to withstand adriamycin therapy. However, its precise function and potential as a therapeutic target require further investigation (76, 90, 91).

Gao et al. demonstrated that circ_0006528 is significantly upregulated in breast cancer tissues compared to adjacent normal tissues and is associated with advanced disease stages and poor patient prognosis. Mechanistically, circ_0006528 functions as a molecular "sponge" for miR-7-5p, a microRNA known for its tumor-suppressive effects. By binding to miR-7-5p, circ_0006528 prevents it from inhibiting its target gene, Raf1. Activated Raf1 phosphorylates MEK1/2 on two serine residues, which converts MEK into its active kinase form. MEK phosphorylates ERK1/2 on Thr202/Tyr204 (ERK1) or Thr185/Tyr187 (ERK2). This dual phosphorylation fully activates ERK, which can then translocate to the nucleus, phosphorylate transcription factors (such as ELK1, c-Fos, c-Myc), and regulate cytosolic substrates controlling proliferation, differentiation, or survival. Through this circ_0006528/miR-7-5p/Raf1 axis, cells experience enhanced MAPK/ERK signaling. This activation promotes breast cancer cell growth, invasion, and metastasis. Functional studies showed that circ_0006528 enhances DNA synthesis and tumor cell aggressiveness, while its downregulation induces G2 phase cell cycle arrest and increases cell death in breast cancer cells. These findings suggest that circ_0006528 plays a crucial role in breast cancer

ARTICLE IN PRESS

progression by modulating the miR-7-5p/Raf1/MAPK/ERK axis, making it a potential biomarker and therapeutic target in breast cancer management (76).

The study further reveals the molecular mechanism underlying the oncogenic role of circ_0006528, particularly its function as a ceRNA or molecular sponge for miR-7-5p. By sponging miR-7-5p, circ_0006528 prevents miR-7-5p from suppressing its target gene, Raf1, thereby activating the MAPK/ERK signaling pathway. This activation leads to the development, progression, and migration of breast cancer cells (76, 92).

5.1.2. circ-CEP128

Among the growing list of identified circular RNAs (circRNAs), circ-CEP128 has emerged as a significant player, particularly in the context of cancer and cellular signaling. Several studies have highlighted the involvement of circ-CEP128 in various cancers, often acting as an oncogene, contributing to tumor development and progression. Circ-CEP128 is overexpressed in bladder cancer tissues and blood samples, with its expression levels higher in advanced tumor stages and cases with lymph node metastasis. Functionally, circ-CEP128 acts as a "sponge" for miR-145-5p, directly binding to this microRNA and reducing its availability. MiR-145-5p targets and negatively regulates MYD88, a protein overexpressed in bladder cancer and linked to the MAPK signaling pathway (72, 73). The overexpression of circ-CEP128 lowers miR-145-5p and enhances MYD88. Once upregulated, MYD88 recruits IRAK kinases (IRAK1/4), which phosphorylate and activate TRAF6. TRAF6 ubiquitination leads to recruitment and activation of downstream kinases, including TAK1, which can phosphorylate MAPKKs (MKKs). TAK1 phosphorylates MKKs, such as MKK4/7 (for JNK) or MEK1/2 (for ERK). MKKs then phosphorylate MAPKs (ERK, JNK, or p38) on conserved Thr/Tyr residues in their activation loops. Activated MAPKs translocate to the nucleus and

ARTICLE IN PRESS

phosphorylate transcription factors like AP-1 (c-Fos/c-Jun), NF-κB, and others. Therefore, this pathway facilitates the tumor progression.

Silencing circ-CEP128 increases miR-145-5p levels, leading to downregulation of MYD88 and suppression of MAPK signaling. This results in inhibited cell viability and mobility, induction of G0/G1 cell cycle arrest, and increased apoptosis. Functional assays, including wound healing and migration tests, demonstrated that circ-CEP128 silencing significantly impairs bladder cancer cell migration through the miR-145-5p/MYD88/MAPK axis. These findings suggest that targeting circ-CEP128 could serve as a promising therapeutic strategy to inhibit bladder cancer progression by modulating this signaling pathway (72).

5.1.3. circ_0074027

Gao et al. demonstrated that circ_0074027 is upregulated in non-small cell lung cancer (NSCLC) and contributes to tumor progression by promoting cell growth, migration, and metastasis while inhibiting apoptosis. Mechanistically, circ_0074027 functions as a molecular sponge for miR-185-3p, reducing its availability and thereby increasing the expression of downstream oncogenes BRD4 and MADD. MADD functions as an adaptor protein linking extrinsic apoptotic signals (via TNF receptor family) to MAPK pathway activation. Overexpression of MADD can enhance ERK phosphorylation, resulting in boosted cell proliferation and reduced apoptosis. Mechanistically, MADD interacts with Ras or Raf complexes and facilitates the phosphorylation cascades along the MAPK axis. In vitro experiments showed that overexpression of circ_0074027 enhanced proliferation and invasive behaviors in NSCLC cell lines, whereas silencing circ_0074027 suppressed these malignant traits. These findings suggest that circ_0074027 plays a crucial oncogenic role in NSCLC through the miR-185-3p/BRD4/MADD pathway and may serve as a promising therapeutic target (93).

ARTICLE IN PRESS

5.1.4. hsa_circ_0002476

In cancer cells, hsa_circ_0002476 increases proliferation, migration, and invasion, which suggests it contributes to tumor growth and metastasis. Several studies indicate that hsa_circ_0002476 may significantly enhance the malignant progression of NSCLC. On the other hand, hsa_circ_0002476 inhibits apoptosis, which leads to cancer cell survival. It is believed that this anti-apoptotic effect contributes to tumor progression and resistance to therapy. Through miRNA sponging, hsa_circ_0002476 modulates the expression of target genes, thereby influencing various signaling pathways, such as the MAPK pathway. Despite the lack of direct links between the MAPK pathway and circRNAs, the modulation of microRNAs by circRNAs significantly impacts many cellular pathways, including the MAPK pathway. Therefore, by the action of hsa_circ_0002476 working as a micro RNA sponge, it does indeed affect the MAPK pathway (94).

5.1.5. hsa_circ_0000190

Hsa_circ_0000190, derived from the ZKSCAN1 gene, is significantly upregulated in NSCLC tissues and cell lines. It facilitates tumor progression by reinforcing the EGFR-MAPK/ERK cascade, which is critical for tumor cell proliferation, survival, and migration. EGFR activation enhances C190 expression via a MAPK/ERK-dependent mechanism, and conversely, its expression is reduced by MEK1/2 inhibitors or EGFR knockdown. Overexpression of C190 upregulates ERK1/2 phosphorylation, therefore establishing a self-reinforcing positive feedback loop to maintain oncogenic signaling regardless of EGFR mutation status. CRISPR/Cas13a-mediated knockdown of C190 reduces ERK1/2 phosphorylation and tumor cell proliferation and migration both in vitro and in vivo (77).

Moreover, C190 contributes to immune evasion by facilitating the upregulation of soluble PD-L1 and promotes cell cycle progression by upregulating cyclin-dependent kinases, further enhancing the

ARTICLE IN PRESS

aggressiveness of NSCLC (95). Taken together, all these findings position C190 as a representative paradigm for the circRNA-mediated reinforcement of MAPK, in which circRNAs amplify the MAPK cascade through feedback-transcriptional loops and sustain malignant phenotypes (96).

5.1.6. circ-MAPK4

Circular RNA MAPK4 (circ-MAPK4), originating from exon 2 of the MAPK4 gene, is markedly upregulated in glioma tissues compared to normal brain tissue. Its circular structure confers resistance to RNase R digestion and leads to predominant cytoplasmic localization, characteristic of many functional circRNAs. It is important to note that circ-MAPK4 is distinct from the MAPK family and MAPK1 (ERK2) or the canonical ERK1/2 pathway. Circ-MAPK4 promotes glioma progression by acting as a ceRNA that sponges miR-125a-3p, a microRNA known for its tumor-suppressive role through inhibition of the p38/MAPK signaling pathway. By sequestering miR-125a-3p, circ-MAPK4 prevents the microRNA from suppressing p38/MAPK phosphorylation, thereby inhibiting apoptosis and enhancing glioma cell proliferation, migration, and survival. Experimental silencing of circ-MAPK4 results in increased apoptosis, reduced cell proliferation, and decreased tumor growth both in vitro and in vivo, underscoring its critical role in glioma pathophysiology. These findings position circ-MAPK4 as a promising therapeutic target for this aggressive brain tumor (97).

5.1.7. CircRNA NRIP1

CircRNA NRIP1 (Nuclear Receptor-Interacting Protein 1) is highly expressed and tumorigenic in renal carcinomas, esophageal squamous cell cancers, and notably papillary thyroid carcinoma (PTC). Studies show its overexpression correlates with advanced tumor stages and increased malignancy in PTC. CircRNA NRIP1 promotes PTC progression by sponging tumor-suppressor miR-195-5p, preventing its protective effects and enabling cancer cell growth and spread. Additionally, CircRNA NRIP1 activates key carcinogenic

ARTICLE IN PRESS

pathways, including MAPK. Experimental evidence from cell cultures and mouse models confirms its role in promoting tumor development, highlighting its potential as a diagnostic biomarker and therapeutic target in PTC (78).

5.1.8. hsa_circ_0005909

Circular RNA hsa_circ_0005909 derived from the XPR1 gene through a process known as back-splicing. It is a closed-loop RNA molecule, meaning it lacks free 5' and 3' ends, which makes it more stable than linear RNAs and resistant to exonuclease degradation. Circ_0005909 is primarily located in the cytoplasm of cells, where it functions as a molecular "sponge" for microRNAs, regulating gene expression at the post-transcriptional level (98). Hsa_circ_0005909 has been identified as a key regulator in the progression of osteosarcoma (OS) through multiple mechanisms. One study revealed that circ_0005909 promotes OS progression by functioning as a molecular sponge for miR-936, which in turn regulates the expression of High Mobility Group Box 1 (HMGB1). This interaction enhances OS cell viability, colony formation, migration, invasion, and epithelial-mesenchymal transition (EMT), ultimately contributing to tumor growth and metastasis. Inhibition of circ_0005909 was shown to suppress these malignant behaviors both in vitro and in vivo, indicating its potential as a therapeutic target for OS treatment (98).

A study revealed an oncogenic role of circ_0005909 in osteosarcoma (OS) via the miR-338-3p/HMGA1 axis. Circ_0005909 was found to be upregulated in OS tissues and cell lines, acting as a molecular sponge for miR-338-3p. Knockdown of circ_0005909 reduced cell viability and colony formation. HMGA1 was identified as a direct target of miR-338-3p; its protein levels decreased following circ_0005909 knockdown, but this effect was reversed by inhibiting miR-338-3p. Additionally, circ_0005909 knockdown suppressed the phosphorylation of ERK, indicating its function in activating MAPK-ERK pathway, which is overactivated in OS cells. This inhibition was reversed by

ARTICLE IN PRESS

HMGA1 overexpression, suggesting that circ_0005909 promotes these signaling pathways through HMGA1 (81).

5.1.9. hsa_circ_0006117

In pancreatic cancer tissues, Hsa_circ_0006117 expression was significantly increased, according to Liu et al. The gene maps to protein tyrosine phosphatase receptor type A (PTPRA). This study's key finding suggests that hsa_circ_0006117 plays a crucial role in pancreatic cancer development and progression. This result may be of great importance for oncology as it may enable the development of novel biomarkers and therapeutic targets for PC. We made this inference by conducting an integrated analysis of differentially expressed circRNAs in PC, according to data from two Gene Expression Omnibus (GEO) datasets. Due to its circular structure and its high resistance to RNase R degradation, hsa_circ_0006117 displays excellent structural stability, enabling its preferential cytoplasmic localization, where it exerts its oncogenic activity (83, 99, 100).

To promote PC development, hsa_circ_0006117 functions as a ceRNA to compete with miR-96-5p. The binding traps miR-96-5p, reducing its inhibitory effect on KRAS, a key oncogene in PC. As a result, the expression of KRAS is elevated, which results in the activation of the KRAS/MAPK pathway (101-103). This signaling pathway drives tumor cell proliferation, migration, and invasion. Experimental downregulation of hsa_circ_0006117 using siRNA significantly reduced the malignancy of pancreatic cancer cells. This was confirmed by decreased proliferation (CCK-8 and colony formation assays) and diminished invasiveness and migration (wound healing and transwell assays). Knockdown of hsa_circ_0006117 also reduced KRAS mRNA and protein levels, and suppressed MAPK pathway activity, as evidenced by reduced phosphorylation of MEK1/2 and ERK1/2. Overexpression of KRAS partially restored malignant phenotypes and MAPK pathway activity in

ARTICLE IN PRESS

hsa_circ_0006117-silenced pancreatic cancer cells. Therefore, hsa_circ_0006117 is considered a promising therapeutic target and biomarker for pancreatic cancer due to its critical role in pathogenesis via the KRAS/MAPK signaling pathway (83).

5.1.10. hsa_circRNA_101705

The TXNDC11 gene on chromosome 16 produces the circular RNA hsa_circRNA_101705 (circTXNDC11), which is highly stable due to its closed-loop structure and predominantly localized in the cytoplasm. CircTXNDC11 is overexpressed in renal cell carcinoma (RCC) tissues and cell lines, correlating with advanced TNM stages and lymph node metastasis. It promotes RCC progression by activating the MAPK/ERK signaling pathway through upregulation of MEK and ERK phosphorylation, enhancing cancer cell proliferation, invasion, and tumor growth. Knockdown of circTXNDC11 suppresses these oncogenic behaviors both in vitro and in vivo, and its effects are reversed by the ERK inhibitor SCH772984. These findings position circTXNDC11 as a promising biomarker and therapeutic target in RCC (84).

5.1.11. hsa_circ_0003204

Circular RNA hsa_circ_0003204 is produced by reverse splicing, where the downstream splice acceptor joins the upstream splice donor to form a closed loop. Its circularity has been confirmed using PCR and Sanger sequencing. This circular RNA has been identified as a key regulator of the progression of cervical cancer (CC). It is significantly upregulated in human CC tissues and cell lines compared with surrounding normal tissues. The hsa-circ-0003204 molecule enhances cell growth, migration, and metastasis while simultaneously suppressing apoptosis. Conversely, knockdown of hsa_circ_0003204 inhibited cell growth, reduced migration and invasion, and increased apoptosis in vitro. Western blot analysis showed that overexpression of the active substance increased phosphorylation of key

ARTICLE IN PRESS

signaling elements of MAPK, including ERK and p38, while knockdown resulted in reduced phosphorylation. According to *in-vivo* xenograft studies, mice implanted with CC cells expressing hsa_circ_0003204 had noticeably larger tumors in terms of both volume and weight. According to these results, hsa_circ_0003204 may be a useful biomarker and therapeutic target for the management of cervical cancer (85).

5.1.12. CircRNA UBAP2

Circular RNA UBAP2 (circUBAP2), encoding ubiquitin-associated protein 2, is a critical regulator in various cancers and acts as a ceRNA. CircUBAP2 can sponge tumor-suppressor miRNAs to upregulate oncogenes, thereby promoting tumor progression, metastasis, and drug resistance. In prostate cancer (PCa), circUBAP2 enhances tumor growth via the miR-1244–MAP3K2–MAPK pathway. Due to its widespread upregulation and central role in oncogenic pathways, circUBAP2 is a promising biomarker and therapeutic target across multiple cancer types, underpinning ongoing research efforts to develop novel cancer treatments (86).

5.1.13. CircRAD23B

CircRAD23B (hsa_circ_0087862) is derived from the RAD23B gene at chr9:110068659-110081160 and is significantly upregulated in multiple cancer types, including NSCLC (87), ovarian cancer (104), and esophageal cancer (105). Quantitative real-time PCR (qRT-PCR) confirmed that its expression is elevated in tumor tissues compared to normal tissues across these malignancies.

In NSCLC, CircRAD23B is overexpressed in cancerous lung tissues and cell lines. Its upregulation correlates with lymph node invasion, lower differentiation grade, and shorter overall survival. The study revealed that CircRAD23B, functioning as a substrate for the competing ceRNA sponging miR-142-3p, leads to increased MAP4K3, a key regulator of the MAPK signaling pathway. This finding underscores the functional significance of

ARTICLE IN PRESS

CircRAD23B in cancer progression. Western blot analysis confirmed that the knockout of CircRAD23B reduces the phosphorylation of ERK1, JNK, and p38, resulting in the inactivation of the MAPK pathway. This inactivation highlights the potential therapeutic effect of targeting CircRAD23B. Functional tests, including CCK-8 viability, colony formation, and transwell invasion assays, showed that knockdown of CircRAD23B inhibits the proliferation and motility of tumor cells. In vivo, xenograft models have also confirmed that inhibition of CircRAD23B slows tumor growth (87).

5.1.14. Hsa_circ_0002124

According to the report, NUSAP1 is a target of miR-122 involved in cell cycle processes associated with HCC progression (106). Significant increases in NUSAP1 expression were also observed in HCC cells and tissues, and increased NUSAP1 levels correlated with shorter survival in HCC samples (107). The study by Ribbeck et al. They found that NuSAP1, a protein involved in stabilizing microtubules and in spindle assembly (108), was associated with the progression of cancer. In a study by Fang et al., it was found that hsa_circ_0002124 was significantly upregulated compared to normal liver cells in HCC tissues and cell lines, particularly in HepG2, Huh7, 97L, and 97H cells. The results of functional assays demonstrated that overexpression of hsa_circ_0002124 significantly enhances tumor growth, while knockdown induces apoptosis and arrests the cell cycle at the G1 phase. The study confirmed the oncogenic role of hsa_circ_0002124 in hepatic cancer by increasing uncontrolled cell proliferation and resistance to apoptosis (88, 109).

Hsa_circ_0002124 increases HCC progression by acting as sponges for key miRNAs regulating oncogenic proteins, thereby activating the MAPK signaling pathway. Its overexpression increases MAPK activity and c-Myc expression, while knockdown reduces them. Functional assays showed that hsa_circ_0002124 significantly influences cancer cell viability, proliferation,

ARTICLE IN PRESS

apoptosis, and cell cycle progression. Bioinformatics analyses confirmed its involvement in cancer drug response pathways, supporting its potential as a biomarker for diagnosis of early HCC and a target for novel therapies (88).

5.1.15. CircFAT1

CircFAT1 is a stable circRNA derived from exon 2 of the FAT1 gene, which is involved in cell adhesion, migration, and polarity. Due to its circular structure, circFAT1 is resistant to degradation and functions differently depending on cancer type, acting either as a tumor suppressor or oncogene. In NSCLC, circFAT1 is overexpressed and linked to poor prognosis. It promotes immune evasion by increasing regulatory T cell ($CD4^+$ and $Foxp3^+$) infiltration while suppressing cytotoxic $CD8^+$ T cells. Mechanistically, circFAT1 sponges miR-30e-5p to upregulate USP22, enhancing tumor proliferation and metastasis. In cervical cancer, circFAT1 drives progression by interacting with miR-409-3p, leading to increased CDK8 expression and activation of ERK1/2 and p38 MAPK pathways. Silencing circFAT1 reduces cell proliferation, invasion, and tumor growth both in vitro and in vivo. Overall, circFAT1 plays complex, context-dependent roles in cancer biology and represents a promising target for future research and therapeutic interventions (89, 110-113).

ARTICLE IN PRESS

5.2. Tumor suppressor circRNAs

5.2.1. CircRNA 0001313

CircRNA 0001313 (circ-0001313) is a key regulator in several cancers, including colon cancer and NSCLC (**Figure 3**). It mainly functions as a ceRNA for miRNA sponging to modulate gene expression and signaling pathways. In colon cancer, circ-0001313 is highly expressed and promotes tumor growth by sponging miR-510-5p, which upregulates AKT2 and activates the PI3K/Akt/mTOR pathway. This pathway enhances cell proliferation, survival, and resistance to apoptosis. In NSCLC, circ-0001313 drives tumor

ARTICLE IN PRESS

progression via the miR-452/HMGB3/ERK/MAPK axis. By binding miR-452, it increases HMGB3 expression, activating the ERK/MAPK pathway and promoting cancer cell proliferation, migration, and invasion. Overexpression of circ-0001313 increases ERK1/2 and p38 MAPK phosphorylation, confirming its oncogenic role. Overall, circ-0001313 is a promising biomarker and therapeutic target. Targeting it or its downstream pathways could provide new cancer treatment strategies (82).

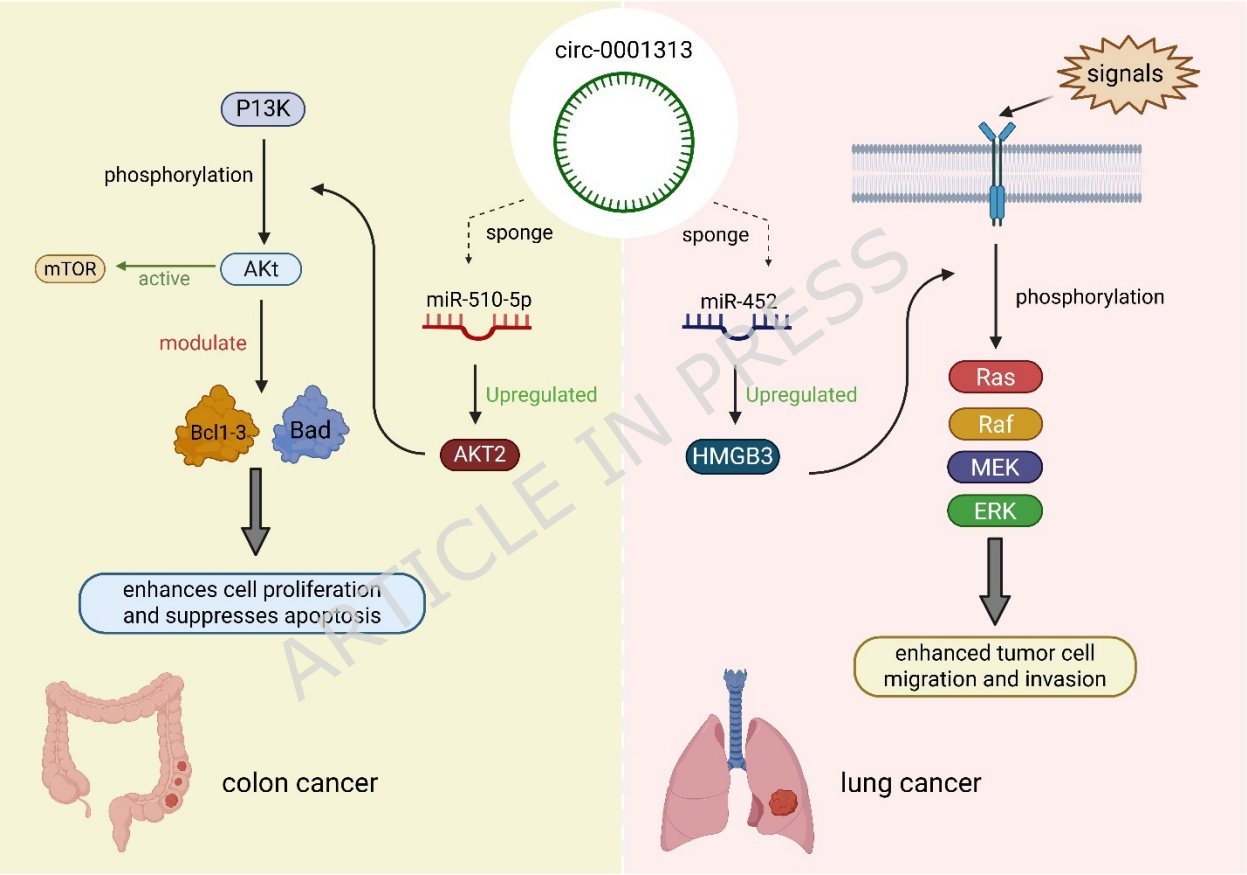


Figure 3. A schematic illustration of circ-0001313's role in colon and lung cancer development. Circ-0001313 acts as a sponge for miR-510-5p in colon cancer (left), increasing AKT2 levels and the P13K/AKT pathway activation. This activation affects Bcl-1, Bcl-2, and Bcl-3, as well as Bad, promoting cell proliferation while reducing apoptosis via mTOR signaling. Circ-0001313 sponges miR-452 in lung cancer (right), leading to the overexpression of HMGB3, which enhances the

ARTICLE IN PRESS

phosphorylation of the Ras/Raf/MEK/ERK signaling cascade, thereby boosting tumor cell motility and invasion in response to extracellular signals.

5.2.2. hsa_circRNA_0000567

CircSETD3 (hsa_circ_0000567) is a circular RNA derived from exons 2–6 of the SETD3 gene on chromosome 14q32.2. Its circular structure confers stability and resistance to RNase R digestion. CircSETD3 acts mainly as a molecular sponge for miRNAs such as miR-421 and miR-641, regulating targets like BMF and PTEN to influence cell proliferation, apoptosis, and tumor growth. It is downregulated in tumors such as HCC, cholangiocarcinoma, and bladder cancer, where its low expression correlates with poor prognosis, indicating a tumor suppressor role. CircSETD3 notably modulates the MAPK signaling pathway through the circSETD3/miR-421/MAPK14 (p38 MAPK) axis in HCC. By binding miR-421, circSETD3 prevents suppression of MAPK14, leading to increased MAPK14 expression. This upregulation reduces proliferation markers (Cyclin D1, PCNA) and inhibits tumor growth and progression. Functional assays, including dual-luciferase reporter tests and rescue experiments, support this mechanism. In vivo xenograft models showed that circSETD3 overexpression results in smaller tumors, higher MAPK14 levels, decreased proliferation, and reduced EMT marker expression (N-cadherin, vimentin), indicating suppressed metastasis. Overall, circSETD3 functions as a critical tumor suppressor regulating cancer cell development via MAPK14 and represents a promising therapeutic target in HCC and other cancers with dysregulated MAPK signaling (79).

5.2.3. CircSLC8A1

circSLC8A1, a circular RNA with a covalently closed-loop structure produced by back-splicing of the SLC8A1 gene, has been the focus of numerous investigations in cancer, particularly in prostate, breast, and bladder cancer

ARTICLE IN PRESS

(80). Notably, circSLC8A1 has been found to suppress PCa development via modulating PTEN, as demonstrated by Lu et al. (114). This promising role of circSLC8A1 in inhibiting PCa progression highlights its therapeutic potential. CircSLC8A1 expression is closely associated with the clinical and histological stages of PCa, with reduced expression observed in PCa tissues and cell lines. CircSLC8A1 upregulation has been shown to suppress cell migration, invasion, and proliferation (114). Wang et al. discovered that circSLC8A1 acts as a miRNA sponge, directly interacting with miR-21 and modulating its function (80). This regulatory role of circSLC8A1 is a key aspect of its potential as a tumor suppressor.

Importantly, the circSLC8A1/miR-21 interaction has been linked to cancer-promoting pathways such as the chemokine signaling pathway and the MAPK signaling pathway, as well as to Gene Ontology (GO) terms related to cell migration and proliferation regulation. These findings underscore the potential of circSLC8A1 to function as a tumor suppressor by modulating these pathways and thereby inhibiting PCa cell growth and progression (80, 115, 116).

ARTICLE IN PRESS

6. Clinical Relevance and Translational Potential

CircRNAs have found at relatively high levels in body fluids such as saliva, plasma, serum, and exosomes (5, 117), making them as promising candidates for noninvasive liquid biopsy biomarkers in cancer. Circ-MAPK4 is markedly upregulated in glioma tissues and correlates with advanced disease and poor prognosis. By sponging miR-125a-3p, it activates p38/MAPK signaling and enhanced glioma cell proliferation and survival (71). Its detection in tumor tissue and plasma suggests diagnostic and prognostic value for glioma. Circ_0006528 (circPRELID2) is highly expressed in breast cancer and drives tumor aggressiveness through the circ_0006528/miR-7-5p/Raf1 axis, which

ARTICLE IN PRESS

results in sustained MEK–ERK activation. Elevated circ_0006528 levels correlate with advanced stage and poor survival, which supports its role as a liquid-biopsy biomarker. Circ-CEP128 is overexpressed in bladder cancer tissues and blood samples, where it promotes tumor progression via the miR-145-5p/MYD88/MAPK axis. High circ-CEP128 expression correlates with advanced stage and lymph-node metastasis. This suggests both diagnostic and prognostic value. Hsa_circ_0006117, upregulated in pancreatic cancer, activates the KRAS/MAPK pathway by sponging miR-96-5p, which normally represses KRAS. Its strong association with tumor invasiveness and progression supports its utility as a noninvasive biomarker. Additional MAPK-related circRNAs, including hsa_circ_0005909 in osteosarcoma, hsa_circRNA_101705 (circTXNDC11) in renal carcinoma, and circRAD23B in NSCLC, ovarian, and esophageal cancer, also exhibit diagnostic and prognostic potential by modulating MAPK-ERK or MAP4K signaling cascades.

Beyond diagnostics, targeting circRNAs that modulate MAPK signaling presents new therapeutic opportunities. Silencing circ-MAPK4 in glioma cells suppresses MAPK/ERK activation and leads to decreased proliferation and increased apoptosis. Therefore, this circRNA may act as a therapeutic target in MAPK-driven tumors. Knockdown of circ_0006528 has been reported to inhibit ERK phosphorylation and reduce invasion and migration of cancer cells by further underscoring the potential of circRNA-directed therapy. Similarly, circ-CEP128 interference attenuates MAPK pathway activation which suggests its regulatory role could be exploited for therapy approaches.

ARTICLE IN PRESS

Emerging technologies, including antisense oligonucleotides (ASOs), RNA interference (RNAi), and synthetic circRNA mimics, are being investigated to modulate circRNA expression. Such approaches could enable selective targeting of circRNAs that sustain MAPK signaling. These approaches offer a novel therapeutic avenue for cancers that are characterized by MAPK pathway hyperactivation.

7. Conclusions and future perspectives

In conclusion, the cross-modulation between circRNAs and the MAPK signaling pathway profoundly influences cancer progression, tumor cell growth, invasion, and therapeutic resistance. CircRNAs such as circ-MAPK4, circ_0006528, circ-CEP128, and circ_0006117 regulate MAPK signaling by miRNA sponging or regulation of upstream mediators like Raf1, MYD88, and KRAS. These interactions finally affect MAPK components including ERK, JNK, and p38, and this mechanism is common among different cancers. Conversely, tumor-suppressive circRNAs such as circSETD3 reinforce this regulatory axis by restoring MAPK14 (p38) function and inhibiting malignant progression.

ARTICLE IN PRESS

Importantly, circRNAs may not only regulate but also be regulated by MAPK-driven feedback mechanisms which creates complex bidirectional interactions that remain underexplored. For instance, hsa_circ_0000190 forms a positive feedback loop with the EGFR–MAPK–ERK pathway in NSCLC, in which MAPK activation increases circRNA expression and, in turn, circRNA upregulation further enhances MAPK activity. Circ_0006528, by promoting the miR-7-5p/Raf1/MAPK/ERK axis in breast cancer, and circ-CEP128, which activates MAPK signaling through the miR-145-5p/MYD88 pathway in bladder cancer, may be part of feedback systems that sustain continuous pathway activation. In glioma, circ-MAPK4 regulates the miR-125a-3p/p38-MAPK pathway, while in pancreatic cancer, hsa_circ_0006117

ARTICLE IN PRESS

enhances KRAS/MAPK signaling, which suggest that circRNAs can act both upstream and downstream of MAPK cascades. Likewise, hsa_circ_0005909 in osteosarcoma and circUBAP2 in prostate cancer activate ERK and MAP3K2, respectively. On the other hand, tumor-suppressive circRNAs such as circSETD3, which restores MAPK14 (p38) activity, illustrate the opposite regulatory direction. Together, these examples reveal the complex two-way communication between circRNAs and MAPK components, where circRNAs can both regulate and be regulated by MAPK signaling. Understanding these feedback and feed-forward loops will be essential for explaining how MAPK-related circRNAs maintain tumor growth, invasion, and therapeutic resistance, and for designing precise interventions targeting this regulatory axis. In this regard, RNA-based inhibition approaches, such as siRNA, antisense oligonucleotides, and CRISPR-guided depletion, offer various possibilities to interfere with MAPK hyperactivation by targeting oncogenic circRNAs or restoring tumor-suppressive ones.

Despite these advances, several limitations remain. First, in vitro studies continue to dominate the literature on circRNA-MAPK interactions, with few studies exploring in vivo validation. The specificity of delivery, the safety of long-term use, and the efficiency of delivery for circRNA-targeted therapies, along with several other factors, remain poorly understood. Second, while it is clear that MAPK activation affects circRNA abundance, the upstream regulatory mechanisms that drive the biogenesis of circRNAs under oncogenic MAPK signaling are poorly defined. Third, RNA-based therapies still face significant hurdles to achieve effective and tumor-specific delivery due to off-target activity, immune activation, and intracellular stability. The focus of future research should be on comprehensive in vivo profiling, characterization of upstream MAPK-dependent splicing and circularization events, and developing targeted delivery systems, including lipid nanoparticles or exosome-based vectors. Elucidation of these aspects will be key in translating circRNA-directed interventions into clinically actionable

ARTICLE IN PRESS

therapies. Overall, understanding circRNAs as integral amplifiers of the MAPK signaling cascade gives a common framework for biomarker discovery and therapeutic innovation in cancer.

8. Declarations

Ethical approval
This study does not involve any animal or human experimental models. Hence, ethical approval is not required.

Consent to Participate
Not applicable.

Consent to publish
All authors have read the final version of the manuscript and declared their consent for publication.

ARTICLE IN PRESS

Clinical Trial Number
Not applicable.

Acknowledgements
Not applicable.

Funding
Not applicable.

Availability of data and material
Not applicable.

Competing interests
The authors declare no conflict of interest.

ARTICLE IN PRESS

Reference

1. Rostami Ravari N, Sadri F, Mahdiabadi MA, Mohammadi Y, Ourang Z, Rezaei Z. Ferroptosis and noncoding RNAs: exploring mechanisms in lung cancer treatment. Front Cell Dev Biol. 2025;13:1522873.
2. Garlapati P, Ling J, Chiao PJ, Fu J. Circular RNAs regulate cancer-related signaling pathways and serve as potential diagnostic biomarkers for human cancers. Cancer Cell International. 2021;21(1):317.
3. Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nature Structural & Molecular Biology. 2015;22(3):256-64.
4. Zhang Y, Zhang X-O, Chen T, Xiang J-F, Yin Q-F, Xing Y-H, et al. Circular Intronic Long Noncoding RNAs. Molecular Cell. 2013;51(6):792-806.
5. Verduci L, Tarcitano E, Strano S, Yarden Y, Blandino G. CircRNAs: role in human diseases and potential use as biomarkers. Cell Death & Disease. 2021;12(5):468.
6. Jeck WR, Sharpless NE. Detecting and characterizing circular RNAs. Nature Biotechnology. 2014;32(5):453-61.
7. Zhou Z, Sun B, Huang S, Zhao L. Roles of circular RNAs in immune regulation and autoimmune diseases. Cell Death & Disease. 2019;10(7):503.
8. Aufiero S, Reckman YJ, Pinto YM, Creemers EE. Circular RNAs open a new chapter in cardiovascular biology. Nature Reviews Cardiology. 2019;16(8):503-14.
9. Mehta SL, Dempsey RJ, Vemuganti R. Role of circular RNAs in brain development and CNS diseases. Progress in Neurobiology. 2020;186:101746.
10. Vo JN, Cieslik M, Zhang Y, Shukla S, Xiao L, Zhang Y, et al. The Landscape of Circular RNA in Cancer. Cell. 2019;176(4):869-81.e13.
11. Li J, Sun D, Pu W, Wang J, Peng Y. Circular RNAs in Cancer: Biogenesis, Function, and Clinical Significance. Trends in Cancer. 2020;6(4):319-36.
12. Ju HQ, Zhao Q, Wang F, Lan P, Wang Z, Zuo ZX, et al. A circRNA signature predicts postoperative recurrence in stage II/III colon cancer. EMBO Molecular Medicine. 2019;11(10):e10168.
13. Bach D-H, Lee SK, Sood AK. Circular RNAs in Cancer. Molecular Therapy Nucleic Acids. 2019;16:118-29.
14. Du WW, Yang W, Liu E, Yang Z, Dhaliwal P, Yang BB. Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. Nucleic Acids Research. 2016;44(6):2846-58.
15. Yang Q, Du WW, Wu N, Yang W, Awan FM, Fang L, et al. A circular RNA promotes tumorigenesis by inducing c-myc nuclear translocation. Cell Death & Differentiation. 2017;24(9):1609-20.
16. Legnini I, Di Timoteo G, Rossi F, Morlando M, Briganti F, Sthandier O, et al. Circ-ZNF609 Is a Circular RNA that Can Be Translated and Functions in Myogenesis. Molecular Cell. 2017;66(1):22-37.e9.
17. Ho-Xuan H, Lehmann G, Glazar P, Gypas F, Eichner N, Heizler K, et al. Gene Expression Signatures of a Preclinical Mouse Model during Colorectal Cancer Progression under Low-Dose Metronomic Chemotherapy. Cancers [Internet]. 2021; 13(1).
18. Guo YJ, Pan WW, Liu SB, Shen ZF, Xu Y, Hu LL. ERK/MAPK signalling pathway and tumorigenesis (Review). Exp Ther Med. 2020;19(3):1997-2007.
19. Zhang W, Liu HT. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. Cell Research. 2002;12(1):9-18.

ARTICLE IN PRESS

20. Yuan W, Shi Y, Dai S, Deng M, Zhu K, Xu Y, et al. The role of MAPK pathway in gastric cancer: unveiling molecular crosstalk and therapeutic prospects. Journal of Translational Medicine. 2024;22(1):1142.
21. Cuevas BD, Abell AN, Johnson GL. Role of mitogen-activated protein kinase kinase kinases in signal integration. Oncogene. 2007;26(22):3159-71.
22. Morrison DK. MAP Kinase Pathways. Cold Spring Harbor Perspectives in Biology. 2012;4(11):a011254.
23. McKay MM, Morrison DK. Integrating signals from RTKs to ERK/MAPK. Oncogene. 2007;26(22):3113-21.
24. Shaul YD, Seger R. The MEK/ERK cascade: From signaling specificity to diverse functions. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2007;1773(8):1213-26.
25. Zhang Y, Dong C. Regulatory mechanisms of mitogen-activated kinase signaling. Cell Mol Life Sci. 2007;64(21):2771-89.
26. Weston CR, Davis RJ. The JNK signal transduction pathway. Current Opinion in Genetics & Development. 2002;12(1):14-21.
27. Johnson GL, Nakamura K. The c-jun kinase/stress-activated pathway: Regulation, function and role in human disease. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2007;1773(8):1341-8.
28. Dhanasekaran DN, Reddy EP. JNK signaling in apoptosis. Oncogene. 2008;27(48):6245-51.
29. Cargnello M, Roux PP. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiology and molecular biology reviews. 2011;75(1):50-83.
30. Tchounwou PB, Dasari S, Noubissi FK, Ray P, Kumar S. Advances in our understanding of the molecular mechanisms of action of cisplatin in cancer therapy. Journal of experimental pharmacology. 2021:303-28.
31. Cuenda A, Rousseau S. p38 MAP-Kinases pathway regulation, function and role in human diseases. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2007;1773(8):1358-75.
32. Cuadrado A, Nebreda Angel R. Mechanisms and functions of p38 MAPK signalling. Biochemical Journal. 2010;429(3):403-17.
33. del Barco Barrantes I, Coya JM, Maina F, Arthur JS, Nebreda AR. Genetic analysis of specific and redundant roles for p38alpha and p38beta MAPKs during mouse development. Proc Natl Acad Sci U S A. 2011;108(31):12764-9.
34. Cuadrado A, Nebreda AR. Mechanisms and functions of p38 MAPK signalling. Biochem J. 2010;429(3):403-17.
35. Kyriakis JM, Avruch J. Mammalian MAPK signal transduction pathways activated by stress and inflammation: a 10-year update. Physiological reviews. 2012;92(2):689-737.
36. Cuenda A, Rousseau S. p38 MAP-kinases pathway regulation, function and role in human diseases. Biochim Biophys Acta. 2007;1773(8):1358-75.
37. Corre I, Paris F, Huot J. The p38 pathway, a major pleiotropic cascade that transduces stress and metastatic signals in endothelial cells. Oncotarget. 2017;8(33):55684.
38. Hayakawa M, Hayakawa H, Petrova T, Ritprajak P, Sutavani RV, Jiménez-Andrade GY, et al. Loss of Functionally Redundant p38 Isoforms in T Cells Enhances Regulatory T Cell Induction. J Biol Chem. 2017;292(5):1762-72.
39. Escós A, Risco A, Alsina-Beauchamp D, Cuenda A. p38γ and p38δ mitogen activated protein kinases (MAPKs), new stars in the MAPK galaxy. Frontiers in cell and developmental biology. 2016;4:31.
40. Canovas B, Nebreda AR. Diversity and versatility of p38 kinase signalling in health and disease. Nature reviews Molecular cell biology. 2021;22(5):346-66.
41. Matesanz N, Nikolic I, Leiva M, Pulgarin-Alfaro M, Santamans AM, Bernardo E, et al. p38α blocks brown adipose tissue thermogenesis through p38δ inhibition. PLoS biology. 2018;16(7):e2004455.

ARTICLE IN PRESS

42. Zarubin T, Han J. Activation and signaling of the p38 MAP kinase pathway. Cell research. 2005;15(1):11-8.
43. Obata T, Brown GE, Yaffe MB. MAP kinase pathways activated by stress: the p38 MAPK pathway. Critical care medicine. 2000;28(4):N67-N77.
44. Zhang J, Shen B, Lin A. Novel strategies for inhibition of the p38 MAPK pathway. Trends in pharmacological sciences. 2007;28(6):286-95.
45. Asl ER, Amini M, Najafi S, Mansoori B, Mokhtarzadeh A, Mohammadi A, et al. Interplay between MAPK/ERK signaling pathway and MicroRNAs: A crucial mechanism regulating cancer cell metabolism and tumor progression. Life Sciences. 2021;278:119499.
46. Guo T, Yuan X, Li X, Liu Y, Zhou J. Bone regeneration of mouse critical-sized calvarial defects with human mesenchymal stem cell sheets co-expressing BMP2 and VEGF. Journal of Dental Sciences. 2023;18(1):135-44.
47. Denkert C, Schmitt WD, Berger S, Reles A, Pest S, Siegert A, et al. Expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) in primary human ovarian carcinoma. International Journal of Cancer. 2002;102(5):507-13.
48. Denkert C, Schmitt WD, Berger S, Reles A, Pest S, Siegert A, et al. Expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) in primary human ovarian carcinoma. International journal of cancer. 2002;102(5):507-13.
49. Yuan J, Dong X, Yap J, Hu J. The MAPK and AMPK signalings: interplay and implication in targeted cancer therapy. Journal of Hematology & Oncology. 2020;13(1):113.
50. Yaeger R, McKean MA, Haq R, Beck JT, Taylor MH, Cohen JE, et al. A next-generation BRAF inhibitor overcomes resistance to BRAF inhibition in patients with BRAF-mutant cancers using pharmacokinetics-informed dose escalation. Cancer Discovery. 2024;14(9):1599-611.
51. Burotto M, Chiou VL, Lee J-M, Kohn EC. The MAPK pathway across different malignancies: A new perspective. Cancer. 2014;120(22):3446-56.
52. Hobbs GA, Der CJ, Rossman KL. RAS isoforms and mutations in cancer at a glance. Journal of Cell Science. 2016;129(7):1287-92.
53. Li Q, Yang G, Ren B, Liu X, Tang LQ, Shi Q, et al. ZC3H14 facilitates backsplicing by binding to exon-intron boundary and 3' UTR. Mol Cell. 2024;84(22):4314-33.e9.
54. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA. 2013;19(2):141-57.
55. Ying L, Niannian L, Le Y, Jianjun T, Yinglong W, Meng M. A Brief Review of circRNA Biogenesis, Detection, and Function. Current Genomics. 2021;22(7):485-95.
56. Chen I, Chen C-Y, Chuang T-J. Biogenesis, identification, and function of exonic circular RNAs. WIREs RNA. 2015;6(5):563-79.
57. Zhang X-O, Wang H-B, Zhang Y, Lu X, Chen L-L, Yang L. Complementary Sequence-Mediated Exon Circularization. Cell. 2014;159(1):134-47.
58. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB, Kjems J. The biogenesis, biology and characterization of circular RNAs. Nature Reviews Genetics. 2019;20(11):675-91.
59. Verduci L, Strano S, Yarden Y, Blandino G. The circRNA–microRNA code: emerging implications for cancer diagnosis and treatment. Molecular Oncology. 2019;13(4):669-80.
60. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013;495(7441):333-8.
61. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495(7441):384-8.
62. Su M, Xiao Y, Ma J, Tang Y, Tian B, Zhang Y, et al. Circular RNAs in Cancer: emerging functions in hallmarks, stemness, resistance and roles as potential biomarkers. Molecular Cancer. 2019;18(1):90.

ARTICLE IN PRESS

63. Li G, Yang H, Han K, Zhu D, Lun P, Zhao Y. A novel circular RNA, hsa_circ_0046701, promotes carcinogenesis by increasing the expression of miR-142-3p target ITGB8 in glioma. Biochemical and Biophysical Research Communications. 2018;498(1):254-61.
64. He R, Liu P, Xie X, Zhou Y, Liao Q, Xiong W, et al. circGFRA1 and GFRA1 act as ceRNAs in triple negative breast cancer by regulating miR-34a. Journal of Experimental & Clinical Cancer Research. 2017;36(1):145.
65. Li Z, Yanfang W, Li J, Jiang P, Peng T, Chen K, et al. Tumor-released exosomal circular RNA PDE8A promotes invasive growth via the miR-338/MACC1/MET pathway in pancreatic cancer. Cancer Letters. 2018;432:237-50.
66. Wei J, Li M, Xue C, Chen S, Zheng L, Deng H, et al. Understanding the roles and regulation patterns of circRNA on its host gene in tumorigenesis and tumor progression. Journal of Experimental & Clinical Cancer Research. 2023;42(1):86.
67. Liu Y, Li Z, Zhang M, Zhou H, Wu X, Zhong J, et al. Rolling-translated EGFR variants sustain EGFR signaling and promote glioblastoma tumorigenicity. Neuro-oncology. 2021;23(5):743-56.
68. Wang X, Li J, Bian X, Wu C, Hua J, Chang S, et al. CircURI1 interacts with hnRNPM to inhibit metastasis by modulating alternative splicing in gastric cancer. Proc Natl Acad Sci U S A. 2021;118(33).
69. Sadri F, Hosseini SF, Aghayei A, Fereidouni M, Rezaei Z. The Tumor Suppressor Roles and Mechanisms of MiR-491 in Human Cancers. DNA Cell Biol. 2022;41(9):810-23.
70. Hazari V, Samali SA, Izadpanahi P, Mollaei H, Sadri F, Rezaei Z. MicroRNA-98: the multifaceted regulator in human cancer progression and therapy. Cancer Cell Int. 2024;24(1):209.
71. He J, Huang Z, He M, Liao J, Zhang Q, Wang S, et al. Circular RNA MAPK4 (circ-MAPK4) inhibits cell apoptosis via MAPK signaling pathway by sponging miR-125a-3p in gliomas. Molecular Cancer. 2020;19(1):17.
72. Sun M, Zhao W, Chen Z, Li M, Li S, Wu B, et al. Circular RNA CEP128 promotes bladder cancer progression by regulating Mir-145-5p/Myd88 via MAPK signaling pathway. International journal of cancer. 2019;145(8):2170-81.
73. Hua L, Huang L, Zhang X, Feng H, Shen B. Knockdown of circular RNA CEP128 suppresses proliferation and improves cytotoxic efficacy of temozolomide in glioma cells by regulating miR-145-5p. Neuroreport. 2019;30(18):1231-8.
74. Rezatabar S, Karimian A, Rameshknia V, Parsian H, Majidinia M, Kopi TA, et al. RAS/MAPK signaling functions in oxidative stress, DNA damage response and cancer progression. Journal of cellular physiology. 2019;234(9):14951-65.
75. Pisignano G, Michael DC, Visal TH, Pirlog R, Ladomery M, Calin GA. Going circular: history, present, and future of circRNAs in cancer. Oncogene. 2023;42(38):2783-800.
76. Gao D, Qi X, Zhang X, Fang K, Guo Z, Li L. hsa_circRNA_0006528 as a competing endogenous RNA promotes human breast cancer progression by sponging miR-7-5p and activating the MAPK/ERK signaling pathway. Molecular Carcinogenesis. 2019;58(4):554-64.
77. Ishola AA, Chien C-S, Yang Y-P, Chien Y, Yarmishyn AA, Tsai P-H, et al. Oncogenic circRNA C190 promotes non–small cell lung cancer via modulation of the EGFR/ERK pathway. Cancer Research. 2022;82(1):75-89.
78. Li C, Zhu L, Fu L, Han M, Li Y, Meng Z, et al. CircRNA NRIP1 promotes papillary thyroid carcinoma progression by sponging mir-195-5p and modulating the P38 MAPK and JAK/STAT pathways. Diagnostic pathology. 2021;16:1-11.
79. Xu L, Feng X, Hao X, Wang P, Zhang Y, Zheng X, et al. CircSETD3 (Hsa_circ_0000567) acts as a sponge for microRNA-421 inhibiting hepatocellular carcinoma growth. Journal of Experimental & Clinical Cancer Research. 2019;38:1-15.
80. Wang D, Yan S, Wang L, Li Y, Qiao B. circSLC8A1 acts as a tumor suppressor in prostate cancer via sponging miR-21. BioMed research international. 2021;2021(1):6614591.

ARTICLE IN PRESS

ARTICLE IN PRESS

81. Zhang C, Na N, Liu L, Qiu Y. CircRNA hsa_circ_0005909 promotes cell proliferation of osteosarcoma cells by targeting miR-338-3p/HMGA1 axis. Cancer Management and Research. 2021:795-803.
82. Zhang S, Liu J, Yuan T, Liu H, Wan C, Le Y. Circular RNA 0001313 knockdown suppresses non-small cell lung cancer cell proliferation and invasion via the microRNA-452/HMGB3/ERK/MAPK axis. International Journal of General Medicine. 2020:1495-507.
83. Liu T, Zhou L, He Z, Chen Y, Jiang X, Xu J, et al. Circular RNA hsa_circ_0006117 Facilitates Pancreatic Cancer Progression by Regulating the miR-96-5p/KRAS/MAPK Signaling Pathway. Journal of Oncology. 2021;2021(1):9213205.
84. Yang C-Y, Wang J, Zhang J-Q, Cai H-m. Human circular RNA hsa_circRNA_101705 (circTXNDC11) regulates renal cancer progression by regulating MAPK/ERK pathway. Bioengineered. 2021;12(1):4432-41.
85. Huang X-B, Song K-J, Chen G-B, Liu R, Jiang Z-F, He Y-L. Circular RNA hsa_circ_0003204 promotes cervical cancer cell proliferation, migration, and invasion by regulating MAPK pathway. Cancer Biology & Therapy. 2020;21(10):972-82.
86. Li X, Azhati B, Wang W, Rexiati M, Xing C, Wang Y. Circular RNA UBAP2 promotes the proliferation of prostate cancer cells via the miR-1244/MAP3K2 axis. Oncology Letters. 2021;21(6):486.
87. Zhuang Q, Huang Z, Zhuang W, Hong Y, Huang Y. Knockdown of circ-RAD23B inhibits non-small cell lung cancer progression via the miR-142-3p/MAP4K3 axis. Thoracic Cancer. 2022;13(5):750-60.
88. Fang Z, Fan R, Lu Y, Sun Y, Zhao C, Liu L, et al. Circular RNA hsa_circ_0002124 promotes hepatocellular carcinoma cell proliferation through the MAPK pathway. Translational Cancer Research. 2019;8(2):367.
89. Zhou B, Li T, Xie R, Zhou J, Liu J, Luo Y, et al. CircFAT1 facilitates cervical cancer malignant progression by regulating ERK1/2 and p38 MAPK pathway through miR-409-3p/CDK8 axis. Drug Development Research. 2021;82(8):1131-43.
90. Misir S, Yaman SO, Petrović N, Sumer C, Hepokur C, Aliyazicioglu Y. circRNAs in drug resistance of breast cancer. Oncology Research. 2023;30(4):157.
91. Liu G, Zhang Z, Song Q, Guo Y, Bao P, Shui H. Circ_0006528 contributes to paclitaxel resistance of breast cancer cells by regulating miR-1299/CDK8 axis. OncoTargets and therapy. 2020:9497-511.
92. Mirzaei Z, Barati T, Ebrahimi A, Derakhshan SM, Khaniani MS. The role of mir-7-5p in cancer: function, prognosis, diagnosis, and therapeutic implications. Molecular Biology Reports. 2025;52(1):12.
93. Gao P, Wang Z, Hu Z, Jiao X, Yao Y. Circular RNA circ_0074027 indicates a poor prognosis for NSCLC patients and modulates cell proliferation, apoptosis, and invasion via miR-185-3p mediated BRD4/MADD activation. Journal of cellular biochemistry. 2020;121(3):2632-42.
94. Wang W, Sun H, Ma X, Zhu T, Zhang H. Circ_0002476 regulates cell growth, invasion, and mtDNA damage in non-small cell lung cancer by targeting miR-1182/TFAM axis. Thorac Cancer. 2022;13(20):2867-78.
95. He H, Li T. Hsa_circ_0000190 Promotes NSCLC Cell Resistance to Cisplatin via the Modulation of the miR-1253/IL-6 Axis. Analytical Cellular Pathology. 2024;2024(1):6647810.
96. Rodriguez-Fuguet A, Zhang W-C. Targeting EGFR-steered cancer via erasing a circular RNA. ExRNA. 2022;4.
97. He J, Huang Z, He M, Liao J, Zhang Q, Wang S, et al. Circular RNA MAPK4 (circ-MAPK4) inhibits cell apoptosis via MAPK signaling pathway by sponging miR-125a-3p in gliomas. Molecular cancer. 2020;19:1-17.
98. Ding S, Zhang G, Gao Y, Chen S, Cao C. Circular RNA hsa_circ_0005909 modulates osteosarcoma progression via the miR-936/HMGB1 axis. Cancer cell international. 2020;20:1-12.

ARTICLE IN PRESS

ARTICLE IN PRESS

99. Wei S, Zheng Y, Jiang Y, Li X, Geng J, Shen Y, et al. The circRNA circPTPRA suppresses epithelial-mesenchymal transitioning and metastasis of NSCLC cells by sponging miR-96-5p. EBioMedicine. 2019;44:182-93.
100. Xie F, Huang C, Liu F, Zhang H, Xiao X, Sun J, et al. CircPTPRA blocks the recognition of RNA N 6-methyladenosine through interacting with IGF2BP1 to suppress bladder cancer progression. Molecular cancer. 2021;20:1-17.
101. Santana-Codina N, Roeth AA, Zhang Y, Yang A, Mashadova O, Asara JM, et al. Oncogenic KRAS supports pancreatic cancer through regulation of nucleotide synthesis. Nature communications. 2018;9(1):4945.
102. Liu Y, Feng W, Gu S, Wang H, Zhang Y, Chen W, et al. The UCA1/KRAS axis promotes human pancreatic ductal adenocarcinoma stem cell properties and tumor growth. American Journal of Cancer Research. 2019;9(3):496.
103. Yu S, Lu Z, Liu C, Meng Y, Ma Y, Zhao W, et al. miRNA-96 suppresses KRAS and functions as a tumor suppressor gene in pancreatic cancer. Cancer research. 2010;70(14):6015-25.
104. Wang H, Zhang Y, Miao H, Xu T, Nie X, Cheng W. CircRAD23B promotes proliferation and carboplatin resistance in ovarian cancer cell lines and organoids. Cancer Cell International. 2024;24(1):42.
105. Lan X, Liu X, Sun J, Yuan Q, Li J. CircRAD23B facilitates proliferation and invasion of esophageal cancer cells by sponging miR-5095. Biochemical and Biophysical Research Communications. 2019;516(2):357-64.
106. He B, He Y, Shi W, Gong S, Chen X, Xiao J, et al. Bioinformatics analysis of gene expression alterations in microRNA-122 knockout mice with hepatocellular carcinoma. Molecular Medicine Reports. 2017;15(6):3681-9.
107. Roy S, Hooiveld GJ, Seehawer M, Caruso S, Heinzmann F, Schneider AT, et al. microRNA 193a-5p regulates levels of nucleolar-and spindle-associated protein 1 to suppress hepatocarcinogenesis. Gastroenterology. 2018;155(6):1951-66. e26.
108. Ribbeck K, Groen AC, Santarella R, Bohnsack MT, Raemaekers T, Köcher T, et al. NuSAP, a mitotic RanGTP target that stabilizes and cross-links microtubules. Molecular biology of the cell. 2006;17(6):2646-60.
109. Iyer J, Moghe S, Furukawa M, Tsai M-Y. What's Nu (SAP) in mitosis and cancer? Cellular signalling. 2011;23(6):991-8.
110. Takaki W, Konishi H, Shoda K, Arita T, Kataoka S, Shibamoto J, et al. Significance of circular FAT1 as a prognostic factor and tumor suppressor for esophageal squamous cell carcinoma. Annals of Surgical Oncology. 2021;28(13):8508-18.
111. Li J, Liu Y, Zeng W, Wu Y, Ao W, Yuan X, et al. The Relationship Between the Expression of circFAT1 and Immune Cell in Patients with Non-Small Cell Lung Cancer. International journal of general medicine. 2023:4943-51.
112. Dong W, Zhang H, Dai Y, Zhou Y, Luo Y, Zhao C, et al. circRNA circFAT1 (e2) Elevates the Development of Non-Small-Cell Lung Cancer by Regulating miR-30e-5p and USP22. BioMed Research International. 2021;2021(1):6653387.
113. Yao Y, Li X, Cheng L, Wu X, Wu B. Circular RNA FAT atypical cadherin 1 (circFAT1)/microRNA-525-5p/spindle and kinetochore-associated complex subunit 1 (SKA1) axis regulates oxaliplatin resistance in breast cancer by activating the notch and Wnt signaling pathway. Bioengineered. 2021;12(1):4032-43.
114. Lu Q, Liu T, Feng H, Yang R, Zhao X, Chen W, et al. Circular RNA circSLC8A1 acts as a sponge of miR-130b/miR-494 in suppressing bladder cancer progression via regulating PTEN. Molecular cancer. 2019;18:1-13.
115. Folini M, Gandellini P, Longoni N, Profumo V, Callari M, Pennati M, et al. miR-21: an oncomir on strike in prostate cancer. Molecular cancer. 2010;9:1-12.

ARTICLE IN PRESS

116. Pfeffer SR, Yang CH, Pfeffer LM. The role of miR-21 in cancer. Drug development research. 2015;76(6):270-7.
117. Kahkesh S, Khoshnazar SM, Gholinezhad Y, Esmailzadeh S, Hosseini SA, Alimohammadi M, et al. The potential role of circular RNAs -regulated PI3K signaling in non-small cell lung cancer: Molecular insights and clinical perspective. Pathol Res Pract. 2024;257:155316.

ARTICLE IN PRESS