Received: 20 October 2022 | Accepted: 5 December 2022

DOI: 10.1002/cai2.50

REVIEW

CANCER INNOVATION

Emerging roles of circular RNAs in the invasion and metastasis of head and neck cancer: Possible functions and mechanisms

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Funding information
Fund of Sichuan Provincial Department of Science and Technology, Grant/Award Numbers: 2022YFS0039, 2022YFSY0058; National Natural Science Foundation of China, Grant/Award Numbers: 81730030, 81771086, 81902784; the CAMS Innovation Fund for Medical Sciences (CIFMS), Grant/Award Number: 2019-I2M-5-004; China Postdoctoral Science

Abstract

Head and neck cancer (HNC) is the seventh most prevalent malignancy worldwide in 2020. Cancer metastasis is the main cause of poor prognosis in HNC patients. Recently, circular RNAs (circRNAs), initially thought to have no biological function, are attracting increasing attention, and their crucial roles in mediating HNC metastasis are being extensively investigated. Existing studies have shown that circRNAs primarily function through miRNA sponges, transcriptional regulation, interacting with RNA-binding proteins (RBPs) and as translation templates. Among these functions, the function of miRNA sponge is the most prominent. In this review, we summarized the reported circRNAs involved in HNC metastasis, aiming to elucidate the regulatory relationship between circRNAs and HNC metastasis. Furthermore, we summarized the latest advances in the epidemiological information of HNC metastasis and the tumor metastasis theories, the biogenesis, characterization and functional mechanisms of circRNAs, and their potential clinical applications. Although the research on circRNAs is still in its infancy, circRNAs are expected to serve as prognostic markers and

Abbreviations: CCLs, C-C motif chemokine ligands; CDR1AS, cerebellar degeneration-related protein 1 antisense transcript; ceRNAs, competing endogenous RNAs; circRNAs, circular RNAs; ciRNAs, intronic circRNAs; CSCs, cancer stem cells; ecircRNAs, exonic circRNAs; EGF, epidermal growth factor; EIciRNAs, exon-intron circRNAs; ELF3, E74-like ETS transcription factor 3; EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; f-circRNAs, fusion circRNAs; HGF, hepatocyte growth factor; HIPK3, homeodomain-interacting protein kinase 3; HNCs, head and neck cancers; HNSCC, head and neck squamous cell carcinoma; LCa, laryngeal carcinoma; LSCC, laryngeal squamous cell carcinoma; LUAC, lung adenocarcinoma; MDR1, multidrug resistance 1; MMPs, matrix metalloproteinases; MRP1, multidrug resistance protein 1; ncRNAs, noncoding RNAs; NPC, nasopharyngeal carcinoma; NSCLS, nonsmall cell lung cancer; OSCC, oral squamous cell carcinoma; pre-mRNAs, precursor mRNAs; RBPs, RNA-binding proteins; RNA-seq, RNA sequencing; TGFBR2, transforming growth factor-β receptor II; TSCC, tongue squamous cell carcinoma; VEGF, vascular endothelial growth factor.

Shouyi Tang and Luyao Cai contributed equally to this study.

Foundation, Grant/Award Number: 2019M650247

effective therapeutic targets to inhibit HNC metastasis and significantly improve the prognosis of HNC patients.

KEYWORDS
circRNA, head and neck cancer, invasion, metastsais

1 | INTRODUCTION

Head and neck cancer (HNC) is the seventh most prevalent cancer globally in 2020. Moreover, there were more than 1.51 million new cases and approximately 510,000 deaths [1]. The definition of HNC primarily includes cancers in multiple sites of the head and neck, such as the paranasal sinuses, nasal cavity, oral cavity, pharynx, larynx, salivary glands, and thyroid [2]. Among them, head and neck squamous cell carcinoma (HNSCC) is the main type, mainly including squamous cell carcinoma involving the oral cavity, pharynx and larynx, accounting for more than 90% of HNCs [3]. Despite advances in various therapeutic approaches, outcomes have not improved in recent decades [4]. It is widely accepted that HNC is characterized by tumor invasiveness and metastasis as the main cause of poor prognosis [4, 5].

Cancer metastasis, the process by which cancer cells spread from a primary lesion to a secondary site in the body, is the most lethal feature of cancer [6]. Many factors participate in the regulation of tumor metastasis and interact to form a large-scale regulatory system. Recent studies have shown that epithelial-mesenchymal transition (EMT), autophagy and cancer stem cells are major influencers that promote cancer cell metastasis [7]. EMT, the process by which epithelial cells lose their epithelial characteristics and acquire mesenchymal ones, is the most critical factor [7]. Extensive studies have shown that the EMT program contributes pathologically to cancer progression, including cancer cell migration, invasion, metastasis, and resistance to therapy [8, 9]. Further studies have shown that EMT is not a binary process, but occurs in different cellular states, and that these different EMT stages correlate with the metastatic potential of cancer cells [10].

Autophagy is believed to play a crucial role in maintaining cellular homeostasis. However, a growing number of studies have shown that autophagy is also involved in tumor metastasis [11]. Typically, autophagy protects genome stability and prevents tumor cells formation [12]. When tumors are formed, autophagy can inhibit metastasis in the early stages of tumor metastasis [13]. However, autophagy can provide advanced cancer cells with the metabolic energy and substances required for continued growth by inducing autophagy and recycling of intracellular components, thereby promoting the ability of tumor cells to adapt to limited nutrients and hypoxic conditions, thereby promoting tumor metastasis [11]. There is evidence that cancer stem cells (CSCs) are involved in tumor metastasis. Furthermore, CSC-targeted therapy is a promising strategy for tumor treatment [14].

Circular RNAs (circRNAs) are a subclass of noncoding RNAs (ncRNAs) that arise from a noncanonical splicing event named back-splicing [15]. They were first identified in viroids more than 40 years ago [16]. Unfortunately, however, they were considered to be byproducts arising from aberrant splicing events [17]. Recently, with the rapid development of high-throughput RNA sequencing (RNA-seq) and circRNA-specific bioinformatics algorithms, many circRNAs have been identified [18–21], and their important roles in regulating cancer development and progression have been extensively studied [22]. Up to now, dysregulation of circRNA expression in various cancer subtypes has been reported [23–25], and circRNAs seem to be involved in the whole process of tumorigenesis, development and metastasis. Therefore, as a new type of ncRNAs, circRNAs have attracted more and more attention from researchers around the world.

Meanwhile, knowledge of the functions and molecular mechanisms of circRNAs in cancer has been accumulated. More importantly, the correlation between some circRNAs, that is, ciRS-7, circPARD3, circMMP9, circHIPK3, circCRIM1, hsa_circRNA_102002, circTGFβR2 and circRNA_0000140, and HNC metastasis has been extensively studied [26–34]. Due to their key regulatory roles in HNC metastasis, circRNAs are expected to be used as prognostic indicators and therapeutic targets for HNC. The purpose of this article is to review recent studies on the roles of these aberrantly expressed circRNAs in regulating EMT, migration, invasion, and metastasis of HNC and to generate new insights into their possible functions and mechanisms.

2 | EPIDEMIOLOGICAL DATA OF HNC METASTASIS

HNC is a relatively broad type of cancer that can be subdivided into multiple cancers. Among them, different types of HNC exhibit different epidemiology, pathophysiology, treatment and metastasis rates.

As mentioned above, HNSCC is the most dominant pathological type in HNC [3]. What's more, the incidence of HNSCC continues to rise and is projected to increase by 30% by 2030 [35]. The prognosis of HNSCC patients depends on many variables, including stage, site of disease, HPV status, and so forth. The 5-year overall survival (OS) rate may be 70%–90% in stage I-II patients. However, patients with stage III–IV disease generally have a poorer prognosis. Some highly malignant diseases, such as locally advanced laryngeal carcinoma, have a 5-year survival rate of approximately 40% [36]. In addition, patients with recurrence and/or metastases have a poor prognosis, with a median OS of less than 1 year achieved with currently available first-line therapies [37]. Notably, this study demonstrated that more than 65% of HNSCC patients had recurrent or metastatic disease (or both) [38]. Therefore, elucidating the possible functions and mechanisms is crucial to improve therapeutic efficacy.

Despite originating from similar cell and tissue types, nasopharyngeal carcinoma (NPC) differs markedly from other epithelial HNCs in terms of epidemiology, pathology and treatment [39]. Compared with other HNCs, NPC is relatively uncommon, and the overall incidence worldwide is gradually decreasing [40]. However, due to insidious and aggressive symptoms, more than 70% of NPC patients were first diagnosed with locally advanced disease [41, 42]. It is noteworthy that once distant metastases develop, patients usually have a poor prognosis, even with the appropriate treatment [43, 44]. Distant metastases from NPC are commonly seen in the bone, lung, liver and retroperitoneal lymph nodes [45–47]. Based on the discovery of distant metastases, the median survival may be 30.8 months [47].

Thyroid cancer, a female-predominant endocrine malignancy, is the most common HNC, accounting for approximately 3.0% of all newly diagnosed cancers worldwide in 2020 [1]. Papillary thyroid carcinoma (PTC) is the major subtype of thyroid cancer, accounting for more than 85% of thyroid cancer cases [48]. PTC is characterized by good differentiation and is generally considered to be of low malignancy, so most PTC patients have a good prognosis after treatment [49]. Nonetheless, some patients with lymph node metastases, epidural invasion, distant metastases and other high-risk conditions still exhibited poor clinical outcomes [50]. Studies in this field have shown that more than 30% of patients with PTC may develop cervical lymph node metastases [51], and less commonly, 2.6%–3.7% of patients may develop distant metastases, typically involving the lungs [52]. Remarkably, Lung metastases occurred in 7%–30% of children and adolescents under the age of 20 years, compared with only about 4% in adults [53, 54]. Furthermore, the recurrence of PTC is significantly increased in the presence of metastases [55].

3 | BIOGENESIS, CHARACTERIZATION, AND FUNCTIONAL MECHANISMS OF CIRCRNAS

Most eukaryotic precursor mRNA (pre-mRNA) transcripts must undergo alternative splicing to remove introns and join exons to form mature mRNA [56, 57]. Typically, splicing joins an upstream 5′ splice site with a downstream 3′ splice site across an intron, but many pre-mRNAs can be processed by back-splicing, where a downstream 3′ splice site joins an upstream 5′ splice site to form circRNAs [58]. Furthermore, these molecules can be classified into three major categories: exonic circRNAs (ecircRNAs), intronic circRNAs (ciRNAs) and exon-intron circRNAs (EIciRNAs). As the names suggest, the first two circRNAs are generated from exons and introns of the pre-mRNAs, and EIciRNAs are composed of exons and introns [19]. In addition to the circRNAs mentioned above, the existence of a special type of circRNA called fusion circRNA (f-circRNA) has been demonstrated, which arises from fusion genes formed by cancer-associated chromosomal translocations [59].

circRNAs have several notable features. Most critically, circRNAs are exceptionally stable and less susceptible to RNA exonuclease cleavage compared with linear mRNAs due to the circular structure [19, 60, 61]. The underlying mechanisms involved in circRNA metabolism are only beginning to be elucidated [62, 63]. Furthermore, circRNAs have been previously observed to be highly conserved [64, 65]. Due to the redundancy of the genetic code, the third position of the codon is usually not highly conserved. Previous studies have established that the third position of codon is more conserved in some circRNAs than in exons that are not part of circRNAs [61]. Accumulating evidence showed that many circRNAs exhibit specific expression in different cells [18, 66], tissues [67] and developmental stages [68], suggesting that they have important biological functions.

Generally speaking, circRNAs can exist in the nucleus or cytoplasm, and different subcellular localizations may determine various biological functions of circRNAs. Except for intron-containing circRNAs, most circRNAs are exported into the cytoplasm after their biogenesis [69]. Therefore, circRNAs primarily function in the cytoplasm. Most biologically functional circRNAs act as competing endogenous RNAs (ceRNAs) in the cytoplasm. ceRNA patterns are defined as miRNA sponges that bind miRNAs and prevent them from

binding and repressing their target mRNAs [70–72]. Some circRNAs can also function by interacting with proteins [73–75]. In addition to the above, several studies have demonstrated that circRNAs can be used as templates for protein translation [76–80] or as sources of pseudogene generation [81]. As for circRNAs in the nucleus, some of them are thought to regulate transcription, alternative splicing and chromatin interactions [82–84].

4 | OVERVIEW OF CIRCRNAS INVOLVED IN HNC METASTASIS

4.1 | circRNAs that play a positive regulatory role in HNC metastasis

So far, various circRNAs have been confirmed to positively affect the metastasis, EMT, migration and invasion of HNC. Here, we summarize representative circRNAs and discuss the current understanding of the molecular mechanisms behind these processes.

4.1.1 | ciRS-7

Circular RNA ciRS-7 (ciRS-7) is a class of endogenous circRNA that was first identified in 2011 in the cerebellar degeneration-related protein 1 antisense transcript (CDR1AS) [72]. Therefore, ciRS-7, also named CDR1AS or CDR1NAT, functions to regulate RNA transcription, downstream gene expression, and protein production [85]. In addition, several studies have reported that ciRS-7 may be an endogenous RNA-linked ciRS-7 that competes with miR-7 [61, 72]. As one of the most famous circRNAs, ciRS-7 has been identified to be involved in the progression of various malignancies [86–88].

In the field of HNC, a study showed that ciRS-7 may also act as a modulator of the metastatic ability of laryngeal squamous cell carcinoma (LSCC). Zhang and colleagues found that ciRS-7 was associated with advanced TNM stages, poorly differentiated tumors, and lymph node metastasis in LSCC [26]. In vitro experiments showed that ciRS-7 knockdown regulates the expression of CCNE1 and PIK3CD by sponging miR-7, thereby inhibiting the proliferation, EMT, migration and invasion of LSCC cell lines [26]. In addition, in vivo experiments showed that ciRS-7 can also increase cellular CCNE1 and PIK3CD levels, which are beneficial to tumor proliferation and metastasis [26]. Likewise, Dou et al. have demonstrated that ciRS-7 can also promote the metastatic progression of oral squamous cell carcinoma (OSCC) by sponging miR-7 [27]. They found that overexpression of ciRS-7 increased the expression of RAF-1 and PIK3CD, leading to activation of the MAPK/AKT signaling pathway [27]. Afterwards, these in vitro results were reprised by in vivo experiments. More importantly, they found that LV-ciRS-7-infected cells on encysted reactive fibrous tissue were more aggressive and angiogenic, indicating enhanced metastatic capacity [27].

4.1.2 | CircPARD3

As mentioned in "Background," according to recent investigations, autophagy plays a double-edged sword role in cancer metastasis. A recent study showed that p62, an autophagy substrate whose levels are inversely correlated with autophagic flux [89], was significantly upregulated in LSCC tissues, indicating autophagy inhibition in LSCC [28]. Through further RNA-sequencing and high-content screening, an upregulated circular RNA circPARD3 (circ_00043) was identified to inhibit autophagy in LSCC tissues. The high expression of circPARD3 was closely related to advanced TNM staging and poor prognosis of LSCC patients. Moreover, circPARD3 was found to promote cell proliferation, migration and invasion in LSCC cell lines and inhibit autophagy by activating the PRKCI-Akt-mTOR pathway through sponging miR-145-5p [28]. Then in vivo experiments made the results more convincing. The researchers found extremely low expression levels of PRKCI, phosphorylated Akt, phosphorylated mTOR, p62, and the EMT markers N-cadherin and vimentin in circPARD3 knockdown xenograft tumors [28].

4.1.3 | CircMMP9

Matrix metalloproteinases (MMPs) are a group of endopeptidases that disrupt all basement membranes and extracellular matrix molecules [90]. Previous studies have identified MMPs as important players in each step of the metastatic cascade [91]. In HNSCC, high levels of MMP2, MMP9, and MMP13 have been reported to be associated with invasion, metastasis and poor prognosis [92–94]. Furthermore, MMP9 has been clearly shown to be a key regulator of OSCC cell migration and invasion across basement membrane [95].

According to the circBase database (http://circbase.org/), MMP9 can generate three different circRNAs: hsa_circ_0001161, hsa_circ_0060571 and hsa_circ_0001162 (circ-MMP9). Moreover, Xia et al. found that only circMMP9 was significantly upregulated in OSCC tissues [29]. Functional assays then revealed that circMMP9 can promote OSCC metastasis in vitro and

in vivo. In follow-up experiments, they found that circMMP9 can regulate the expression of AUF1 by sponging miR-149 [29]. More importantly, AUF1 is a key regulator of mRNA stability and/or translation [96]. Taken together, they found that circMMP9 can promote OSCC metastasis by regulating the stability of its host gene through miR-149 and AUF1 [29].

4.1.4 | CircHIPK3

CircHIPK3 (hsa_circ_0000284) is derived from homeodomain-interacting protein kinase 3 (HIPK3) and like most circRNAs, is predominantly localized in the cytoplasm [97]. Furthermore, circHIPK3 is the most abundant in the brain, especially in the cerebellum [98]. Importantly, there is evidence that circHIPK3 plays a critical role in the initiation and progression of various cancers [97].

Recently, circHIPK3 was considered to play a key role in HNSCC metastasis. Wang et al. found that circHIPK3 was significantly increased in OSCC tissues and cell lines. Furthermore, the expression level of circHIPK3 was closely correlated with TNM staging and tumor grade [99]. Then in vitro experiments showed that circHIPK3 can act as a sponge of miR-124 to promote OSCC proliferation, and more detailed mechanisms await further study [99].

Likewise, Zhao et al. found that circHIPK3 was highly expressed in NPC tissues and cell lines. Furthermore, both in vivo and in vitro experiments showed that circHIPK3 can promote the progression and metastasis of NPC [30]. Mechanistically, circHIPK3 can act as a sponge for miR-4288, whose direct target gene is E74-like ETS transcription factor 3 (ELF3) [30], which has been identified as an oncogene in previous studies [100–102].

4.1.5 | CircCRIM1

CircCRIM1 (hsa_circ_0002346) dysregulation was originally detected in lung adenocarcinoma (LUAC) [103]. Researchers found that circCRIM1 can promote the expression of the leukemia inhibitory factor receptor, a well-known tumor suppressor, thereby inhibiting the invasion and metastasis of LUAC [103]. Aside from that, Zhang et al. obtained the same result that circCRIM1 can inhibit LUAC metastasis [104]. Surprisingly, another study showed that circCRIM1 can promote osteosarcoma migration and invasion in vitro [105].

Regarding HNC, circCRIM1 has also been reported to be an oncogene in NPC. Hong et al. used RNA sequencing to show that circCRIM1 was overexpressed in NPC tissues with distant metastasis [31]. In addition, circCRIM1 expression can be an independent prognostic factor and may be a promising biomarker to predict metastasis and chemotherapy benefit in NPC [31]. Subsequently, overexpression of circCRIM1 contributed to cell migration, invasion and EMT in NPC cell lines. FOXQ1 has been reported to play important roles in cell proliferation, motility, EMT and stemness [106]. Further mechanistic studies revealed that circCRIM1 can enhance FOXQ1 expression by sponging miR-422a, thereby promoting NPC metastasis [31]. Furthermore, in an inguinal lymph node metastasis model constructed to fully assess the prometastasis role of circCRIM1 in vivo, the same results as those obtained in in vitro experiments were observed [31].

4.1.6 | Hsa_circRNA_102002

Hsa_circRNA_102002 produced by ubiquitin-specific peptidase 22 (USP22) was overexpressed in PTC tissues by microarray expression profiling [107]. Zhang et al. then found that hsa_circRNA_102002 can improve the capacity of PTC metastasis, as shown by enhanced EMT and PTC cell migration in vitro [32]. Further mechanistic studies revealed a direct interaction between has_circRNA_102002, miR-488-3p and hyaluronic acid synthetase 2 (HAS2) [32]. HAS2, a transmembrane glycosyltransferase and the main extracellular matrix proteoglycan, can provide a hydration matrix to generate gaps in the ECM and promote the migration of tumor cells [108], indicating that hsa_circRNA_102002 mainly affected EMT and migration of PTC cells by regulating HAS2 expression through sponging miR-488-3P [32]. Moreover, the prometastatic function of hsa_circRNA_102002 in vivo has been verified by a mouse lung metastasis model [32].

4.2 | circRNAs that play a negative regulatory role in HNC metastasis

4.2.1 | CircTGFβR2

As a transmembrane serine-threonine kinase, transforming growth factor-β receptor II (TGFBR2) is a putative tumor suppressor gene. It has been reported to be associated with the metastasis of various cancers, such as nonsmall cell lung cancer [109], intestinal cancer [110], pancreatic cancer [111] and others. Furthermore, the low expression of TGFBR2 has been reported to be associated with poor prognosis in NPC patients [112].

Several studies have shown that some circRNAs, such as circTFRC, circENO1 and circAMOTL1, can directly

modulate the expression of host genes through sponging miRNAs [113–115]. Similarly, the circRNA circTGFβR2 generated from TGFβR2 was detected to play a similar role in NPC [33].

Li et al. found that circTGFβR2 was downregulated in NPC tissues, and further analysis showed that the expression level of circTGFβR2 was positively correlated with the clinicopathological features and prognosis of NPC patients [33]. Functionally, both in vivo and in vitro experiments showed that circTGFβR2 can increase the expression of TGFβR2 by sponging miR-107, thereby inhibiting the proliferation and metastasis of NPC [33].

4.2.2 | circRNA_0000140

The Hippo pathway is a novel and conserved tumor suppressor that controls cell proliferation, organ size, tissue regeneration and stem cell self-renewal. LATS2 is a core kinase component of the Hippo pathway and encodes a Ser/Thr protein kinase. The role of LATS2 as a key regulator in the process of cancer metastasis has been extensively studied [116]. Peng et al., have demonstrated that low levels of circRNA_0000140 were significantly associated with higher lymph node metastasis and more advanced TNM stage in OSCC patients. Furthermore, they found that the expression of circ_0000140 and LATS2 were significantly downregulated, while miR-37 was upregulated in OSCC tissues and cell lines, and overexpressed circ_0000140 inhibited OSCC tumorigenesis and metastasis both in vivo and in vitro. Then more experiments confirmed the regulatory axis of circ_0000140/miR-37/LATS2 [34].

4.3 | Potential metastasis-associated circRNAs in HNC

In addition to the above-mentioned circRNAs associated with metastasis, by analyzing clinical data, there was a correlation between the expression levels of some circRNAs and clinicopathological features characterizing HNC advancement, including lymph node metastasis, distant metastasis and TNM stage. In addition, some circRNAs are only involved in regulating EMT, migration and invasion of HNC in vitro. On the contrary, all their prometastatic or antimetastatic effects in vivo are still under-studied and await further studies. Therefore, these circRNAs can be considered as potential metastasis-associated molecules. This chapter will be divided into four parts, corresponding to potential metastasis-associated circRNAs in oral cancer, pharyngeal cancer, laryngeal cancer and thyroid cancer.

4.3.1 | Potential metastasis-associated circRNAs in oral cancer

OSCC is one of the most common oral malignancies [117], and circRNAs in OSCC have been extensively studied [118]. After verifying the negative correlation between hsa_circ_0004491 expression and lymph node metastasis, Li et al. revealed that hsa_circ_0004491 may affect the migration and invasion of OSCC cells by regulating EMT-related proteins [119]. Besides, Gao et al. demonstrated that the low expression of hsa_circ_0092125 was associated with advanced TNM stage, lymph node metastasis, and poor prognosis [120]. Likewise, the expression of hsa_circ_0086414 was significantly downregulated in OSCC tissues and correlated with TNM stage and lymph node metastasis [121]. Furthermore, Su et al. found that downregulation of hsa_circ_0007059 can inhibit OSCC invasion through AKT/mTOR signaling [122]. Compared with paired noncancerous tissues, OSCC tissues showed downregulation of hsa_circ_0055538, hsa_circ_0005379, hsa_circ_0002203 and hsa_circ_0063772 by high-throughput sequencing by the same research team. Furthermore, they have been shown to inhibit the malignant behavior of OSCC. The expression level of p53 signaling pathway-related proteins was confirmed to be related to hsa_circ_0055538 [123]. Moreover, hsa_circ_0005379 may function by regulating EGFR pathway [124]. In contrast, has_circ_0002203 overexpression decreased the expression of MMP9 [125]. As for hsa_circ_0063772, its mechanism remains to be further studied [126].

Furthermore, Deng et al., showed that significantly enhanced lymph node metastasis was associated with increased expression of circRNA_043621 and overexpression of hsa_circRNA_102459 was associated with poorer clinicopathological features in OSCC patients [127]. Another study showed that hsa_circ_0001742 was significantly overexpressed and was closely associated with advanced clinical stage and lymph node metastasis in patients with tongue squamous cell carcinoma (TSCC) [128]. Moreover, further studies demonstrated that hsa_circ_0001742 can regulate the expression of RAB1A, an oncogene involved in various cancers [129], by sponging miR-634 [130]. Besides, hsa_circ_0008898 and circ_0001742 were upregulated in OSCC. Functional assays showed that they can promote OSCC cell proliferation, migration, invasion and EMT through miR-431-5p/ATF3 axis and hsa_circ_0008898/miR-197-5p/RHOA pathway, respectively [131, 132]. Recently, Zhang et al. found that hsa_circ_0002162 can promote cell proliferation and invasion, but repress apoptosis by targeting miR-33a-5p in TSCC cells [133].

In another microarray assay, circPKD2 was significantly reduced in OSCC tissues [134]. In addition,

circPKD2 overexpression can regulate the APC2 expression by acting as a sponge for miR-204-3p, thereby reducing the migration and invasion abilities of SCC15 cells. Moreover, miR-204-3p can increase the expression of metastasis-associated proteins (e.g., c-MYC, Bax, Caspase-3, and MMP-9) [134]. Zhu et al. showed that downregulation of hsa_circRNA_100533 promoted cell proliferation and migration in OSCC cell lines. Subsequently, the has_circRNA_100533-miR-933-GNAS axis was validated [135].

Fucoidan is a fucose-rich natural polysaccharide mainly extracted from brown seaweed and has attracted attention for its anticancer properties [136]. Zhang et al. found that fucoidan negatively affected the migration and invasion of OSCC cells. Meanwhile, circFLNA expression was increased in OSCC cells treated with fucoidan. Thereafter, the migration and invasion abilities of OSCC cells infected with the circFLNA overexpression vector were reduced, suggesting that fucoidan exerts anticancer effects through the interaction with circFLNA [137]. Circulating exosomes have become biomarkers for early detection and diagnosis of cancer patients and provide information on potential regulators of tumor progression and metastasis [138]. Luo et al. successfully identified an overexpressed circRNA named circ_0000199 (has_circ_0000199) in circulating exosomes from OSCC patients, and the expression level of circ_0000199 was closely related to poor survival outcomes in OSCC patients [139].

4.3.2 | Potential metastasis-associated circRNAs in pharyngeal cancer

Shuai et al. found that overexpressed circRNA_0000285 was closely related to lymph node metastasis, distant metastasis, and TNM stage in NPC patients, suggesting that circRNA_0000285 may be an independent prognostic factor for NPC patients [140]. Likewise, the expression of hsa_circRNA_001387 was significantly increased in NPC patients with well-differentiated tumors, lymph node metastasis and distant metastases in peripheral blood samples of radiotherapy patients [141]. In addition, Liu et al., showed that EBV-encoded circRPMS1 was upregulated in metastatic NPC tissues [142]. Furthermore, the knockdown of circRPMS1 suppressed cell proliferation and invasion in EBV-positive NPC cell lines. Further investigating the underlying mechanism, they found that circRPMS1 can promote EMT by sponging multiple miRNAs, including miR-203, miR-31 and miR-451 [142].

circ_0008450 (hsa_circ_0008450) was overexpressed in NPC tissues compared to adjacent noncancerous tissues [143]. Silencing circ_0008450 inhibited cell migration and invasion of NPC cells, which could be neutralized by inhibiting miR-577. Moreover, a dual-luciferase reporter assay further confirmed the circ_0008450/miR-577/CXCL9 pathway in NPC [143]. Likewise, Liu et al. found that circ_0000615 (hsa_circ_0000615) can also promote migration, invasion, and EMT of NPC cells through miR-338-3P/FGF2 axis [144]. In addition, circCTDP1 was upregulated in NPC tissues and cell lines, which can promote cell proliferation, migration and invasion of NPC cells. Further experiments validated the circCTDP1/miR-320b/HOXA10 axis, and HOXA1O can regulate TGFβ2 expression in NPC cells [145].

4.3.3 | Potential metastasis-associated circRNAs in laryngeal cancer

A recent study on LSCC showed that hsa_circ_0042666 was decreased in LSCC tissues and was related to advanced tumor stage, lymph node metastasis and poorer overall survival. Further experiments proved that hsa_circ_0042666 has a positive effect on inhibiting the proliferation and invasion of LSCC cells. Mechanistically, hsa_circ_0042666 was considered to be a sponge for miR-223, which regulates the expression of TGFBR3, thereby inhibiting the progression of LSCC [146].

Wu et al. found that circCORO1C (hg19_circ_0008714) was significantly upregulated in LSCC tissues, and overexpressed circCORO1C was also related to poorer prognosis in PTC. Further experiments revealed a circCORO1C/let-7c-5p/PBX3 axis [147]. Importantly, PBX3 is an important regulator of the EMT signaling network [148]. In addition, hsa_circ_0023028 was upregulated in laryngeal carcinoma (LCa) tissues based on microarray analysis. Furthermore, after the knockdown of hsa_circ_0023028, the migration and invasion abilities of LCa cells were poorer and the expression level of miR-194-5p was higher. Moreover, hsa_circ_0023028 was shown to act as a miR-194-5p sponge to promote the malignant behavior of LCa cells [149]. Fu et al. found that hsa_circ_0057481 can enhance the migration and invasion of LCa cells by downregulating miR-200c and upregulating ZEB1 [150]. Likewise, circRASSF2 was significantly upregulated in LSCC tissues and LSCC cell lines.

Furthermore, circRASSF2 silencing significantly inhibits cell proliferation and migration in vitro. Subsequently, the direct interaction of circRASSF2, miR-302b-3p and IGF-1R was verified by a dual-luciferase reporter assay. Importantly, circRASSF2 was upregulated in serum exosomes from LSCC patients, suggesting that circRASSF2 could be used as a biomarker for early detection and diagnosis [151]. Yi et al. showed that the cell proliferation, migration and invasion and cisplatin sensitivity of LCa cells were significantly inhibited after

knockdown of circ_0004507 or miR-873 overexpression. Subsequently, a direct binding interaction between circ_0004507, miR-873, MDR1, and MRP1 was revealed [152]. Besides this, Yao et al. showed that circRNA-MYLK positively affected cell migration and invasion by sponging miR-145-5p in Hep-2 cells. Moreover, the expression levels of p-MEK and p-ERK, as well as p/t-MEK and p/t-ERK were significantly decreased by knockdown of circRNA-MYLK [153].

4.3.4 | Potential metastasis-associated circRNAs in thyroid cancer

Downregulation of hsa_circ_0137287 was associated with aggressive PTC clinicopathologic features, including lymph node metastasis, advanced T stage and larger tumor size [154]. Low levels of circITCH were associated with lymph node metastasis in PTC patients. Further tests showed that circITCH can bind to miR-22-3p to increase the expression of Cbl proto-oncogene (CBL), an E3 ligase targeting nuclear β-catenin. Finally, upregulated CBL inhibited the activation of the Wnt/β-catenin pathway, thereby inhibiting the progression of PTC [155].

Through high-throughput RNA sequencing, Chu et al. identified a novel overexpressed circRNA, circRUNX1 (hsa_circ_0002360), in PTC tissues [156]. High levels of circRUNX1 were closely associated with advanced clinical stage and lymph node metastasis. CircRUNX1 silencing can inhibit the migration, invasion and proliferation of PTC cells. Further analysis revealed that circRUNX1 acts as a competing endogenous RNA for miR-296-3p, and DDHD2 was confirmed to be a direct target gene of miR-296-3p [156]. Likewise, Yao et al. found that hsa_circ_0058124 was significantly upregulated in invasive PTC tissues, and overexpressed hsa_circ_0058124 was also associated with poor prognosis in PTC. Furthermore, hsa_circ_0058124 was shown to modulate NUMB expression by sponging miR-218-5p and inhibiting NOTCH3/GATAD2A signaling axis in vitro and in vivo [157]. Moreover, Liu et al. found that an overexpressed circular RNA named hsa_circ_0102272 promoted PTC cell migration and invasion. The high expression of hsa_circ_0102272 was significantly associated with poorer TNM stage, histological grade and lymph node metastasis [158]. As a potential prognostic biomarker, the high expression of circ_0067934 was associated with a lower survival rate, stronger lymph node metastasis and higher AJCC stage. Circ_0067934 can accelerate the proliferation, migration and invasion of thyroid cancer cells in vitro and inhibit cell apoptosis. As for the molecular mechanism, circ_0067934 could regulate CXCR1 expression by binding miR-1304 [159].

In addition, it was confirmed in another study that circ_0067934 promotes EMT by activating the PI3K/AKT signaling pathway [160]. Another recent study reported that hsa_circ_0039411 is involved in tumorigenesis and progression of PTC by sponging miR-1179 and miR-1205 [161]. Moreover, ABCA9 and MTA1 were identified as downstream targets of miR-1179 and miR-1205, respectively [161]. Besides that, Zhang et al. found another upregulated circRNA, circ_0005273, whose knockdown inhibited PTC progression due to its regulation of SOX2 through sponging miR-1183 [162]. Apart from that, Pan et al. demonstrated that circ_0025033 positively affected PTC cell proliferation, migration and invasion by acting as a sponge for miR-1231 and miR-1304 [163].

Based on the same microarray analysis (GSE93522), multiple research teams investigated the link between abnormal expression of circRNAs and the progression of PTC. Jin et al. showed that hsa_circ_0004458 expression was related to lymphatic metastasis, distal metastasis and TNM stage [164]. Going a step further, Li et al. found that circPSD3 promoted cell migration and invasion of PTC cells in vitro. Subsequently, a direct interaction between hsa_circ_0004458, miR637 and HEMGN was confirmed. They then found that knockdown of hsa_circ_0004458 decreased phosphorylation levels of PI3K and Akt, which can be reversed by adding anti-miR-637 or HEMGN, suggesting that has_circ_0004458 may enhance the activity of PI3K/Akt pathway [165]. In another study, Zhou et al. found that overexpressed has_circ_0008274 was closely associated with TNM stage and lymph node metastasis. Further analysis revealed that has_circ_0008274 triggers AMPK/mTOR signaling pathway activation and promotes cancer metastasis [166]. The expression level of circZFR was negatively correlated with the clinical severity of PTC. And circZFR was shown to enhance the migration and invasion of PTC cells by acting as a ceRNA targeting miR-1261 to promote the expression of C8orf4 [167]. Likewise, Chen et al. described a regulatory axis in which circNEK6 was proposed to sponge miR-370-3p to increase the expression of frizzled class receptor 8 (FZD8), a cell surface receptor of canonical Wnt signaling pathway [168]. In addition, circNUP214 identified by Li et al. was highly expressed in PTC tissues and cell lines. Moreover, circNUP214 plays an oncogenic role by sponging miR-145 to promote the expression of ZEB2, which is known as a modulator of the EMT process [169]. Apart from that, Cai et al. found that circBACH2 could function as an oncogene through the miR-139-5p/LMO4 axis [170]. Importantly, Bi et al. found that a circular RNA named circRNA_102171 is mainly localized in the nucleus, and circRNA_102171 can promote PTC cell migration and invasion by interacting with CTNNBIP1, while inhibiting apoptosis, and finally weakening the interaction between β-catenin and

CTNNBIP1, thereby, leading to activation of β-catenin pathway through promoting the binding of β-catenin to TCF/LEF [171].

5 | DISCUSSION

Gene dysregulation is a hallmark of cancer. RNA is critical to gene expression and its regulation, whether protein-coding messenger RNA (mRNA) or noncoding RNA that can perform various biological functions at the RNA level [22]. As an emerging class of noncoding RNAs, circRNAs are expressed in almost all cells and tissues [172], and aberrant expression of circRNAs occurs in multiple cancer types [173], suggesting the critical impact of circRNAs on tumorigenesis and cancer progression. Recently, circRNAs have increasingly become a hot topic in cancer research, especially in tumor metastasis [174, 175]. Depending on their subcellular location, circRNAs perform distinct functions, including regulation of gene transcription, miRNA sponges, interactions with RNA-binding proteins (RBPs) and translation [15]. Moreover, the most prominent molecular mechanism of circRNAs is the miRNA sponge

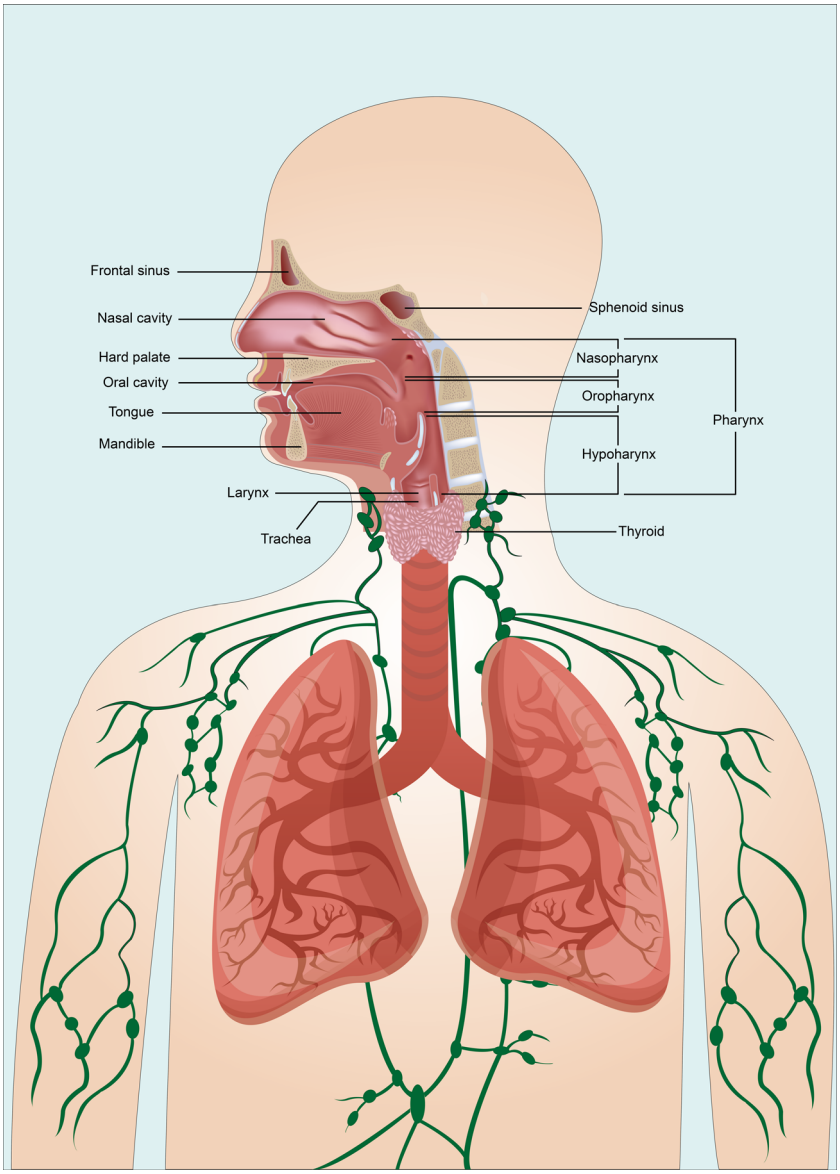

FIGURE 1 The general definition of HNCs primarily includes cancers originating in the oral cavity, nasal cavity, pharynx, larynx, paranasal sinuses, salivary glands and thyroid. The oral cavity includes the lips, buccal mucosa, anterior tongue, floor of the mouth, hard palate, upper and lower gingiva and retromolar. The nasal cavity and paranasal sinuses include the maxillary, ethmoid, sphenoid and frontal sinuses. The pharynx includes the nasopharynx, oropharynx and hypopharynx. The larynx includes the supraglottic larynx, glottic and subglottic larynx. Lung and lymph nodes are the most common metastatic sites of HNC. HNC, head and neck cancers.

as ceRNA [24]. However, great care must be taken when evaluating circRNAs that act as a miRNA sponges. The ceRNA hypothesis remains controversial because of the lack of plausible explanations for how modulating the expression of a single endogenous gene apparently affects miRNA activity at all of its target sites [176], and ceRNA-mediated regulation may depend on the binding site for each miRNA and miRNA abundance [177, 178]. It should be pointed out that compared with other types of cancer, the role and mechanism of circRNAs in HNC metastasis are not clear. Furthermore, there are still some limitations and unresolved issues. For example, the mechanisms involved in circRNA expression and localization still need to be elucidated. Knowledge of circRNA degradation is also limited.

Tumor invasion and metastasis is a complex process involving many factors and multiple pathways. Given its established role in cancer metastasis, EMT has received considerable attention. Downregulation of E-cadherin and upregulation of vimentin can often be found in cells undergoing the EMT process. As a result, cell adhesion is reduced, allowing cell migration and invasion. Notably, the literature has reported a strong relationship between alterations in E-cadherin and vimentin and metastasis of HNSCC [35, 179]. It is now established from various studies that the underlying mechanism of transcriptional repression mediated by Snail (SNAI1 and SNAI2), Zeb (ZEB1 and ZEB2) and basic helix-loop-helix (bHLH: E47 and TWIST) is the dynamic inhibition of CDH1, which encodes E-cadherin [169]. In the field of laryngeal cancer, researchers found that ZEB1 can be upregulated by hsa_circ_0057481 through sponging miR-200c [150]. Likewise, a direct interaction between circNUP214, miR-145 and ZEB2 has been demonstrated in thyroid cancer [180]. Moreover, EMT activation is regulated by multiple signaling pathways [8]. For example, the TGFβ signaling pathway, Wnt/β-catenin signaling pathway, Notch signaling pathway, PI3K/Akt signaling pathway and NF-Kb signaling pathway are all involved in inducing EMT process [181, 182]. TGFβ is a member of a family consisting of three isoforms: TGFβ1, TGFβ2, and TGFβ3 [183]. And a circRNA named circCTDP1 can indirectly regulate the expression of TGFβ2 [145]. Besides, TGFβRs play an important role in modulating the multiple

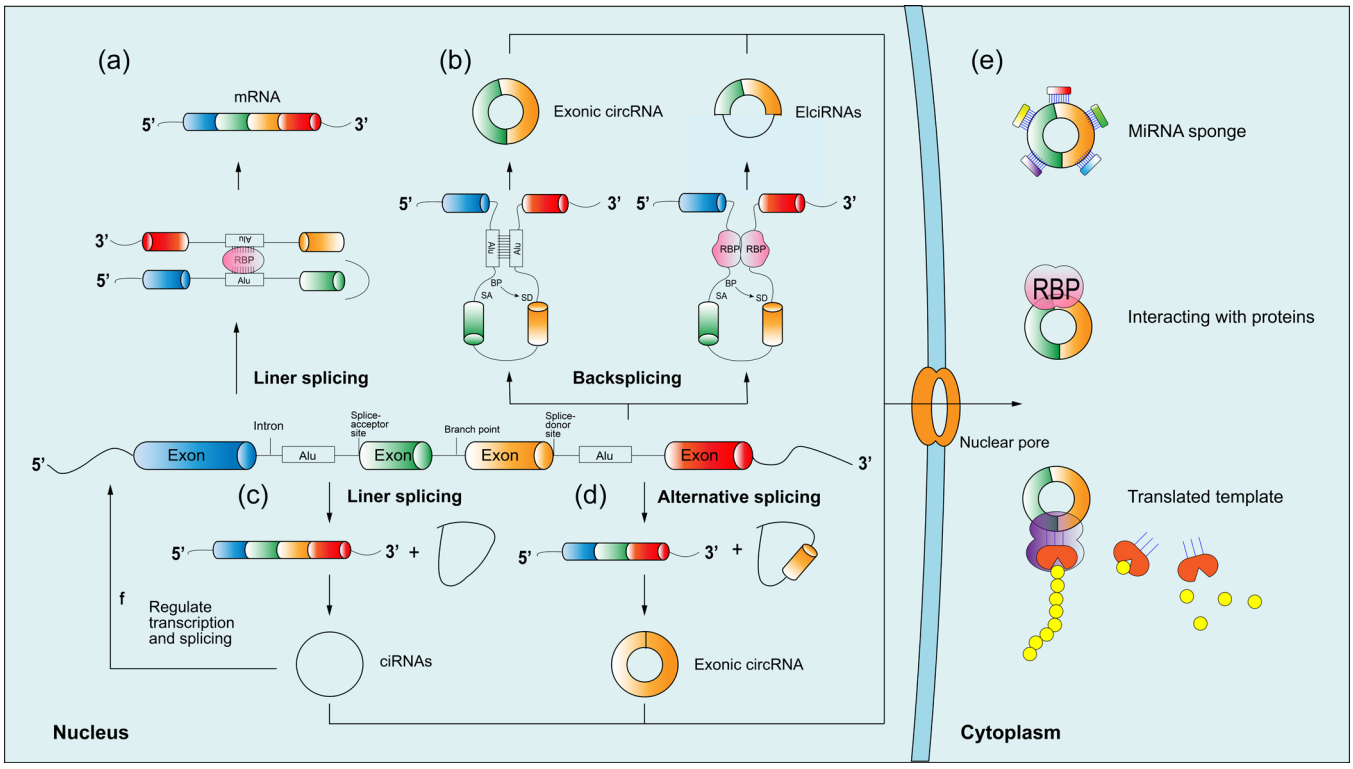

FIGURE 2 circRNA biogenesis and function. (a) Pre-mRNA is canonically spliced into linear RNA by removal of introns. (b) circRNAs are mainly generated by back-splicing. During back-splicing, the upstream branch point attacks the downstream splice donor site, which in turn attacks the upstream splice acceptor site, resulting in exon-intron circRNA (EIcircRNA) or exonic circRNA formation. (c) circRNAs can also be derived from canonical linear splicing through splicing intermediates known as lariat precursors generated by exon skipping events. (d) Another type of exonic circRNAs originates from intronic lariat precursors that escape from debranching during linear splicing. (e) circRNAs mainly function in the cytoplasm through miRNA sponges, interacting with RNA-binding proteins and serving as translation templates. (f) In the nucleus, circRNAs can play a role in regulating transcription and splicing.

actions of TGF-β and in fine-tuning its signaling [184]. circTGFβR2 and hsa_circ_0042666 can act as ceRNA sponges to regulate the expression of TGFβR2 and TGFβR3, respectively [33, 146]. FZD8 has been reported to be one of the most important cell surface receptors in the Wnt signaling pathway [185]. Furthermore, overexpression of circRNA_NEK6 can increase the expression of FZD8 by sponging miR-370-3p [168]. In addition, circRNA_102171 can interact with CTNNBIP1 to activate the Wnt/β-catenin pathway in PTC [171]. Previous studies have noted the importance of the interplay between the GATA family and the NOTCH signaling pathway [186, 187]. A recent study showed that hsa_circ_0058124 can promote PTC progression through the NOTCH3/GATAD2A axis [157]. As for the PI3K/Akt signaling pathway, it was reported to be mediated by several circRNAs: circPARD3, has_circRNA_043621, hsa_circRNA_102459 and hsa_circ_0004458, thereby regulating the progression of HNC [28, 127, 164]. Furthermore, circRNA-MYLK was shown to play a role in the migration and invasion of laryngeal cancer cells by stimulating MEK/ERK and NF-κB cascades [153].

Currently, more academic attention is focused on the tumor microenvironment, which is indispensable in tumor invasion and metastasis [188, 189]. The tumor microenvironment is a complex environment composed not only of tumor cells, but also of many stromal cells, fibroblasts, endothelial cells and immune cells. The tumor microenvironment is constantly changing throughout tumor progression due to changing environmental conditions and oncogenic signals from growing tumor cells. During this dynamic process, various secreted cytokines, chemokines, growth factors and extracellular matrix proteins, such as epidermal growth factor (EGF), hepatocyte growth factor, vascular endothelial growth factor, C-X-C motif chemokine ligands, C-C motif chemokine ligands, interleukins, and MMPs form a complex communication network for intercellular communication [190]. CXCL9, a member gamma subfamily of chemokine proteins, has been implicated in the progression of various malignancies [191, 192]. Overexpressed has_circ_0008450 promotes cell migration and invasion in NPC. Furthermore, miR-577/CXCL9 signaling was shown to mediate the oncogenic function of has_circ_0008450 [143]. Pathological ECM remodeling plays a key role in the metastasis of tumor cells [193]. In the tumor microenvironment, both tumor cells and stromal cells can produce MMPs, which play an important role in extracellular matrix renewal and cancer

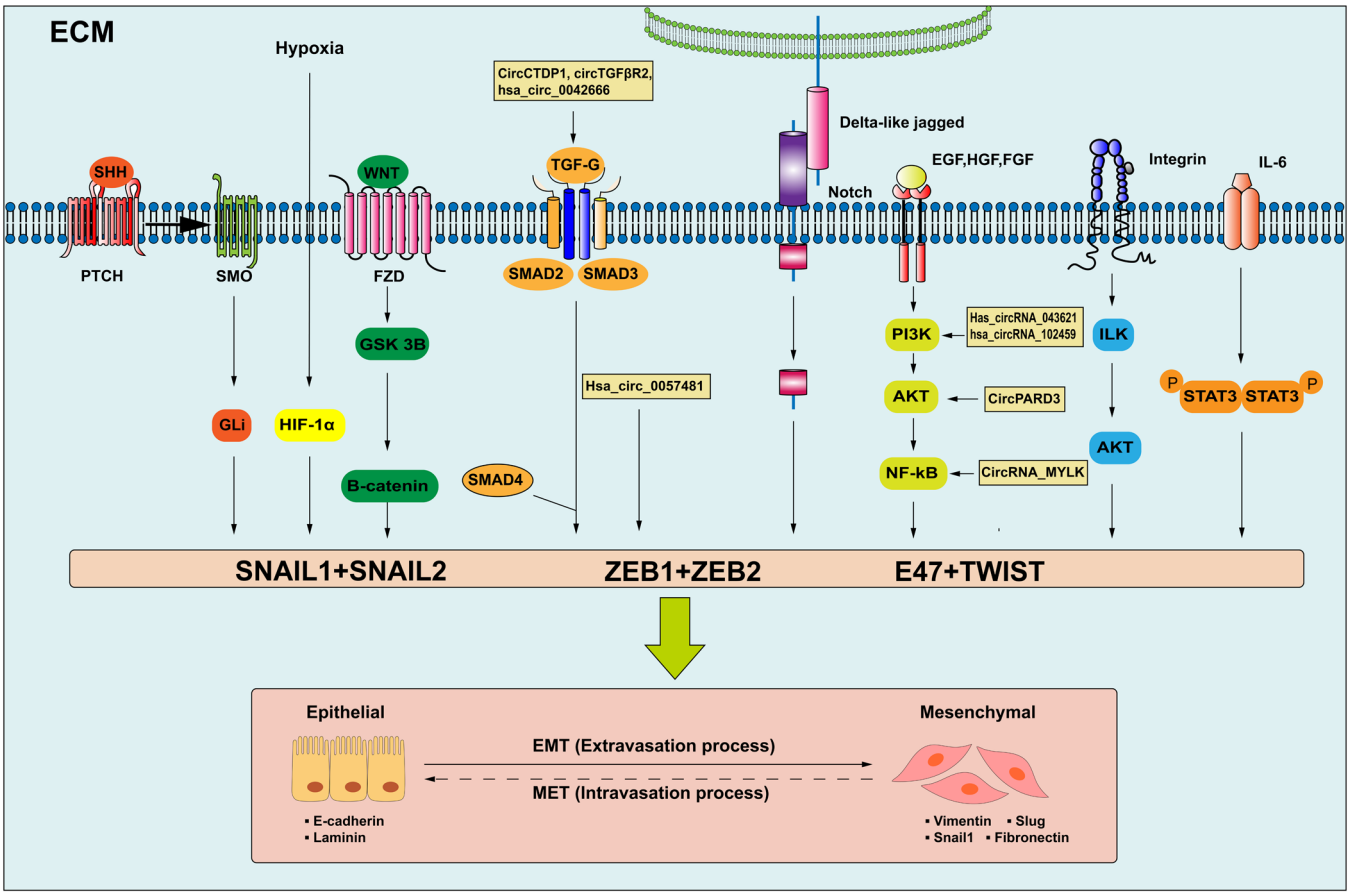

FIGURE 3 Overview of signaling pathways involved in the epithelial-mesenchymal transition process.

TABLE 1 CircRNAs involved in metastasis of HNC.

CircRNA	Gene symbol	Cancer type	Expression change	Association with tumor metastasis	Association with clinicopathological factors	Function	Molecular mechanism	Reference
ciRS-7	CDR1	LSCC	Up	Positive	High level of ciRS-7 was associated with lymph node metastasis and advanced TNM stage	Promote migration, invasion, and EMT	MiRNA sponges (ciRS-7/miR-7/CCNE1/PIK3CD)	[26]
ciRS-7	CDR1	OSCC	Up	Positive	High level of ciRS-7 was associated with advanced TNM stage	Promote migration and invasion,	MiRNA sponges (ciRS-7/miR-7/RAF-1/PIK3CD/MAPK/AKT signaling pathways)	[27]
CircPARD3	PARD3	LSCC	Up	Positive	High level of circPARD3 was associated with advanced T stages, N stages, and clinical stages	Promote migration, invasion, and EMT; Inhibit autophagy	MiRNA sponges (circPARD3/miR-145-5p/PRKCI/Akt-mTOR signaling axis	[28]
CircMMP9	MMP9	OSCC	Up	Positive	High level of circMMP9 was associated with lymph node metastasis and advanced TNM stage	Promote migration and invasion	MiRNA sponges (circMMP9/miR-149/AUF1/MMP9	[29]
CircHIPK3	HIPK3	NPC	Up	Positive	High level of circHIPK3 was associated with advanced TNM stage	Promote migration and invasion	MiRNA sponges (circHIPK3/miR-4288/ELF3)	[30]
CircCRIM1	CRIM1	NPC	Up	Positive	CircCRIM1 was upregulated in NPC patients with distant metastasis	Promote migration, invasion, and EMT	MiRNA sponges (circCRIM1/miR-422a/FOXQ1	[31]
Has_circRNA_102002	USP22	PTC	Up	Positive	High level of has_circRNA_102002 was associated with lymph node metastasis and distant metastasis	Promote migration and EMT	MiRNA sponges (has_circRNA_102002/miR-488-3p/HAS2)	[32]
CircTGFβR2	TGFβR2	NPC	Down	Negative	Low level of circTGFβR2 was associated with advanced T classification, N classification, and clinical stage	Inhibit migration and invasion	MiRNA sponges (circTGFβR2/miR-107/TGFβR2)	[33]

TABLE 1 (Continued)

CircRNA	Gene symbol	Cancer type	Expression change	Association with tumor metastasis	Association with clinicopathological factors	Function	Molecular mechanism	Reference
circRNA_0000140	KIAA0907	OSCC	Down	Negative	Low level of circTGFβR2 was associated with lymph node metastasis and advanced TNM stage	Inhibit migration and invasion	MiRNA sponges (circRNA_0000140/miR-31/LATS2)	[34]
Circ_0000199	AKT3	OSCC	Up	Potentially positive	High level of circ_0000199 was associated with lymph node metastasis and advanced TNM stage	–	–	[139]
Hsa_circRNA_043621	KRT14	OSCC	Up	Potentially positive	High level of has_circRNA_043621 was associated with lymph node metastasis	–	Increase the expression of molecules associated with MAPK and PI3K/Akt signaling pathways	[127]
Hsa_circ_0004491	ORC4	OSCC	Down	Potentially negative	Low level of has_circ_0004491 was associated with lymph node metastasis	Inhibit migration, invasion, and EMT	–	[119]
Hsa_circ_0092125	G6PD	OSCC	Down	Potentially negative	Low level of hsa_circ_0092125 was associated with advanced TNM stage and lymph node metastasis	–	–	[120]
Hsa_circ_0086414	BNC2	OSCC	Down	Potentially negative	Low level of hsa_circ_0086414was associated with advanced TNM stage and lymph node metastasis	–	–	[121]
Hsa_circRNA_102459	MAST1	OSCC	Down	Potentially negative	Low level of hsa_circRNA_102459 was associated with advanced TNM stage and lymph node metastasis	–	Decrease the expression of molecules associated with MAPK and PI3K/Akt signaling pathways	[127]
Hsa_circ_0001742	SMO	TSCC	Up	Potentially positive	High level of hsa_circ_0001742 was associated lymph node metastasis and advanced clinical stage	Promote invasion and EMT	MiRNA sponges (hsa_circ_0001742/miR-634/RAB1A)	[130]

(Continues)

TABLE 1 (Continued)

CircRNA	Gene symbol	Cancer type	Expression change	Association with tumor metastasis	Association with clinicopathological factors	Function	Molecular mechanism	Reference
CircRNA_0000285	HIPK3	NPC	Up	Potentially positive	High level of circRNA_0000285 was associated lymph node metastasis, distant metastasis, and Tumor-Node-Metastasis stage	–	–	[140]
Hsa_circRNA_001387	WHSCI	NPC	Up	Potentially positive	High level of hsa_circRNA_001387 was associated with lymph node metastasis, distant metastasis, and advanced TNM stage	–	–	[141]
CircRPMS1	RPMS1	NPC	Up	Potentially positive	CircRPMS1 was increased in metastatic NPC	Promote invasion and EMT	MiRNA sponges (circRPMS1/miR-200, miR-31, miR-451)	[142]
Hsa_circ_0042666	SUPT6H	LSCC	Down	Potentially negative	Low level of hsa_circ_0042666 was associated advanced tumor stage and lymph node metastasis	Inhibit invasion	MiRNA sponges (hsa_circ_0042666/miR-223/TGFβR3)	[146]
Hsa_circ_0137287	SLC26A7	PTC	Down	Potentially negative	Low level of hsa_circ_0137287 was associated extrathyroidal extension, lymph node metastasis, and advanced T stage	–	–	[154]
CircRUNX1	RUNX1	PTC	Up	Potentially positive	High level of circRUNX1 was associated extrathyroidal extension, lymph node metastasis, and advanced TNM stage	Promote migration and invasion	MiRNA sponges (circRUNX1/miR-296-3p/DDHD2)	[156]
Hsa_circ_0058124	FN1	PTC	Up	Potentially positive	High level of hsa_circ_0058124 was associated extrathyroidal extension, lymph node metastasis, distant metastasis, and advanced TNM stage	Promote migration and invasion	MiRNA sponges (hsa_circ_0058124/miR-218-5p/NUMB/NOTCH3/GATAD2A axis)	[157]

TABLE 1 (Continued)

CircRNA	Gene symbol	Cancer type	Expression change	Association with tumor metastasis	Association with clinicopathological factors	Function	Molecular mechanism	Reference
Circ_0067934	PRKCI	TCa	Up	Potentially positive	High level of circ_0067934 was associated with advanced AJCC stage and lymph node metastasis	Promote migration and invasion	MiRNA sponges (circ_0067934/miR-1304/CXCR1)	[160]
Hsa_circ_0102272	RTN1	TCa	Up	Potentially positive	High level of hsa_circ_0102272 was associated with advanced TNM stage, histological grade, and lymph node metastasis	Promote migration and invasion	–	[158]
Hsa_circ_0004458	PSD3	PTC	Up	Potentially positive	High level of hsa_circ_0004458 was associated with invasion, lymph node metastasis, distal metastasis, and advanced TNM stage	Promote proliferation	MiRNA sponges (hsa_circ_0004458/miR-885-5p/RAC1)	[164]
Hsa_circ_0004458	PSD3	PTC	Up	Potentially positive	–	Promote migration and invasion	MiRNA sponges (hsa_circ_0004458/miR-637/HEMGN/PI3K/Akt pathway	[165]
Hsa_circ_0008274	UGGT2	PTC	Up	Potentially positive	High level of hsa_circ_0008274 was associated with advanced TNM stage and lymph node metastasis	Promote invasion	Promote the activation of the AMPK/mTOR Signaling Pathway	[166]
circZFR	ZFR	PTC	Up	Potentially positive	High level of circZFR was associated with advanced TNM stage and metastasis	Promote migration and invasion	MiRNA sponges (circZFR/miR-1261/C8orf4)	[167]
CircITCH	ITCH	PTC	Down	Potentially negative	Low level of circITCH was associated with lymph node metastasis	Inhibit invasion	MiRNA sponges (circITCH/miR-22-3p/CBL/β-catenin pathway)	[155]

Abbreviations: circRNAs, circular RNAs; EMT, epithelial-mesenchymal transition; HNC, head and neck cancers.

TABLE 2 Potential metastasis-associated circRNAs involved in EMT, migration and invasion of HNC.

CircRNA	Gene symbol	Cancer type	Expression change	Association with EMT, migration, and invasion	Molecular mechanism	Reference
Has_circ_0008898	OAT	OSCC	Up	Promote migration and invasion	MiRNA sponges (has_circ_0008898/miR-197-5p/RHOA)	[131]
Circ_0001742	SMO	TSCC	Up	Promote migration, invasion, and EMT	MiRNA sponges (circ_0001742/miR-431-5P/ATF3)	[132]
Has_circ_0002162	PTK2	TSCC	Up	Promote invasion	MiRNA sponges (has_circ_0002162/miR-33a-5p)	[133]
Has_circ_0055538	RMND5A	OSCC	Down	Inhibit migration and invasion	May affect the progression of OSCC via the p53/Bcl-2/caspase signaling pathway.	[123]
Has_circ_0005379	GDI2	OSCC	Down	Inhibit migration and invasion	May be involved in the regulation of the EGFR pathway	[124]
Has_circ_0002203	CAMTA1	OSCC	Down	Inhibit migration and invasion	–	[125]
Has_circ_0063772	ATXN10	OSCC	Down	Inhibit migration and invasion	–	[126]
CircFLNA	FLNA	OSCC	Down	Inhibit migration and invasion	–	[137]
CircPKD2	PKD2	OSCC	Down	Inhibit migration and invasion	MiRNA sponges (circPKD2/miR-204-3p/APC2)	[134]
Hsa_circRNA_100533	–	OSCC	Down	Inhibit migration	MiRNA sponges (has_circRNA_100533/miR-933/GNAS)	[135]
Hsa_circ_0007059	ZNF720	OSCC	Down	Inhibit migration and invasion	Modulate the AKT/mTOR signaling pathway	[122]
Hsa_circ_0008450	CMTM3	NPC	Up	Promote migration and invasion	MiRNA sponges (hsa_circ_0008450/miR-577/CXCL9)	[143]
Hsa_circ_0000615	ZNF609	NPC	Up	Promote migration, invasion, and EMT	MiRNA sponges (hsa_circ_0000615/miR-338-3p/FGF2)	[144]
CircCTDP1	CTDP1	NPC	Up	Promote migration and invasion	MiRNA sponges (circCTDP1/miRNA-320b/HOXA10/TGFβ2)	[145]
CircCORO1C	CORO1C	LSCC	Up	Promote migration and invasion	MiRNA sponges (circCORO1C/let-7c-5p/PBX3)	[147]
Hsa_circ_0023028	C11orf80	LCa	Up	Promote migration and invasion	MiRNA sponges (hsa_circ_0023028/miR-194-5p)	[149]
Hsa_circ_0057481	PMS1	LCa	Up	Promote migration and invasion	MiRNA sponges (hsa_circ_0057481/miR-200c/ZEB1)	[150]
CircRASSF2	RASSF2	LSCC	Up	Promote migration	MiRNA sponges (circRASSF2/miR-302b-3p/IGF-1R)	[151]
Circ_0004507	SAE1	LCa	Up	Promote migration and invasion	MiRNA sponges (circ_0004507/miR-873/MDR1/MDP1)	[152]
CircRNA-MYLK	MYLK	LCa	Up	Promote migration and invasion	MiRNA sponges (circRNA-MYLK/miR-145-5p/MEK/ERK and NF-κB cascades	[153]
CircRNA_102171	SMURF2	PTC	Up	Promote migration and invasion	Interacting with CTNNBIP1 to activate the Wnt/β-catenin pathway	[171]
CircRNA_NEK6	NEK6	TCa	Up	Promote invasion	MiRNA sponges (circNEK6/miR-370-3p/FZD8/Wnt signaling pathway)	[168]

TABLE 2 (Continued)

CircRNA	Gene symbol	Cancer type	Expression change	Association with EMT, migration, and invasion	Molecular mechanism	Reference
CircNUP214	NUP214	TCa	Up	Promote migration and invasion	MiRNA sponges (circNUP214/miR-145/ZEB2)	[180]
CircBACH2	BACH2	PTC	Up	Promote migration and invasion	MiRNA sponges (circBACH2/miR-139-5p/LMO4)	[170]
Circ_0025033	FOXM1	PTC	Up	Promote migration and invasion	MiRNA sponges (circ_0025033/miR-1231 and miR-1304)	[163]
Hsa_circ_0039411	MMP2	PTC	Up	Promote migration and invasion	MiRNA sponges (hsa_circ_0039411/miR-1179 and miR-1205/ABCA9 and MTA1)	[161]
Circ_0005273	PTK2	TCa	Up	Promote migration and invasion	MiRNA sponges (circ_0005273/miR-1183/SOX2)	[162]

Abbreviations: circRNAs, circular RNAs; EMT, epithelial-mesenchymal transition; HNC, head and neck cancers.

cell migration [194]. A circular RNA derived from MMP9 named circMMP9 was found to increase the stability of its host gene, thereby promoting the metastasis of OSCC [29]. Otherwise, hsa_circ_0039411 produced by MMP2 can promote cell migration and invasion of PTC in vitro [161].

For clinical applicability, experience with the spliceosome inhibitor E7107 [195], H3B-8800 as an oral splicing modulator [196], another splicing modulator RBM39 [197], and miRNA mimics [198–200], in addition to their stability and tissue- or cell type-specific expression, widespread alterations of circRNAs affecting HNC metastasis may be promising therapeutic targets. So far, circRNA-based therapies have only been carried out in preclinical studies. Previous therapies targeting circRNAs mainly include two strategies: gain-of-function and loss-of-function, which usually use circRNA expression plasmids and RNA interference, respectively. Nanoparticle and exosome delivery systems can alleviate the limitations of these strategies, but their safety and efficacy require further in vivo studies. Furthermore, recent advances have shown that Creo-lox system can be used to remove circRNAs in a cell-specific manner. Notably, the CRISPR/Cas13 system exhibited higher specificity and efficiency in knocking down circRNAs compared with RNAi methods. The most promising technology candidate for clinical application is siRNA technology. Furthermore, siRNA nanoparticles have been approved for therapeutic use and are being studied in clinical trials [201].

In summary, circRNAs function in HNC invasion and metastasis through different molecular mechanisms, depending on their subcellular localization. Accumulating evidence indicates that circRNAs can be potential prognostic biomarkers and therapeutic targets. Although the understanding of the precise mechanisms of biogenesis, degradation, cellular localization and function remains limited, the mysteries of circRNAs will finally unravel. We believe the clinical application of circRNAs as biomarkers and therapeutic targets in HNC is promising. (Figure 1–3), (Tables 1 and 2).

AUTHOR CONTRIBUTIONS

Shouyi Tang, Yingqiang Shen, Yu Zhou, and Qianming Chen designed this manuscript. Zhen Wang, Luyao Cai, Dan Pan, and Qing Wang collected and prepared the related papers. Shouyi Tang drafted the manuscript. Zhen Wang, Luyao Cai, and Dan Pan drew the figures. Yingqiang Shen, Yu Zhou, and Qianming Chen supervised and revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

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How to cite this article: Tang S, Cai L, Wang Z, Pan D, Wang Q, Shen Y, et al. Emerging roles of circular RNAs in the invasion and metastasis of head and neck cancer: possible functions and mechanisms. Cancer Innov. 2023;2:463–487. https://doi.org/10.1002/cai2.50