Interaction of circular RNAs with splicing factors in cervical cancer: Modulation, interplay and theranostics (Review)

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Abstract. Cervical cancer (CCa) is a worldwide health concern, particularly in low- and middle-income countries. Human papillomavirus infection is a key risk factor in the development of CCa. Noncoding RNAs (ncRNAs), including microRNAs (miRNAs), circular RNAs (circRNAs) and long ncRNAs (lncRNAs), are important regulators of cancer progression, including CCa, offering potential therapeutic targets. Compared with lncRNAs and miRNAs, circRNAs are the least studied ncRNAs. circRNAs, distinguished by a closed-loop structure and resistance to exonucleases, serve diverse roles in cancer, functioning as miRNA sponges and regulating gene expression. circRNAs are produced primarily by back-splicing and comprise both intronic and exonic sequences. Notably, circRNAs are key regulators of alternative splicing, as they are able to enhance the expression of splicing factors (SFs) by sequestering miRNAs. Despite their importance, the interactions between circRNAs and SFs in CCa remain to be elucidated. The present review highlights the interplay between circRNAs and SFs in CCa pathogenesis; it describes the influence of SFs on circRNA production, the regulatory feedback between circRNAs and SFs, and the potential implications of this interaction in CCa diagnostics and therapeutics. To conduct the present review a targeted literature search was conducted across PubMed, Scopus and Google Scholar using defined search terms to identify peer-reviewed studies published between 2006 and 2024. The findings were synthesized to explore the mechanistic insights and translational implications of circRNA-SF interactions in CCa.

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Contents

1. Introduction

Cervical cancer (CCa) is an important global health issue (1). In 2022, there were ~662,301 new diagnoses of CCa and 348,874 CCa-associated deaths (2); most of these diagnoses and deaths (90%) occurred in low- and middle-income countries (LMICs) (3), with sub-Saharan Africa bearing >80% of the global burden (4). The disparity in mortality rates between high-income countries and LMICs reflects notable differences in access to screening, early diagnosis and timely treatment, with women in LMICs facing disproportionately higher mortality rates despite comparable disease incidence (5).

CCa primarily affects the epithelial lining of the uterine cervix, particularly the squamocolumnar junctions of the ectocervix and endocervix, which are prone to malignant changes. The two most common histological subtypes are adenocarcinoma and squamous cell carcinoma (6,7), comprising ~5 and

~95% of cases, respectively (7,8). Although early diagnosis can lead to effective treatment, CCa remains widespread (9), particularly in LMICs, where it often affects younger women and carries a poor prognosis (10). Notably, CCa is preventable and treatable when detected at an early stage (8,11,12).

A substantial proportion of CCa cases are linked to human papillomavirus (HPV) infection, one of the most common sexually transmitted infections worldwide (8,13). Current therapeutic options include surgery, radiation therapy, chemo-radiation, external beam radiation therapy, chemotherapy and brachytherapy; however, these methods often fall short of desired outcomes and can result in adverse effects (14-16). Consequently, novel diagnostic biomarkers and promising therapeutic targets are needed to detect and treat tumors in cervical tissues.

Noncoding RNAs (ncRNAs), which do not encode proteins, serve key roles in cancer progression and are promising therapeutic targets (17-19). In mammalian cells, non-coding transcripts constitute ~99% of total RNA (20,21). As a subtype of ncRNAs, circular RNAs (circRNAs) are structurally distinct due to their closed-loop configuration, which confers resistance to exonucleases (22,23). circRNAs are typically found in the cytoplasm of eukaryotic cells (24). Unlike linear RNAs that are generated by canonical splicing, circRNAs are produced through back-splicing, where a downstream 3' splice donor site is covalently linked to an upstream 5' splice acceptor site, forming a closed loop (25,26). This process is facilitated by splicing factors (SFs), which regulate reverse splicing (27). For example, the SF Quaking binds to intronic recognition elements near circRNA-forming sites, promoting the generation of circRNAs such as circSHPRH, circSMAD2 and circSMARCA5; these molecules are implicated in epithelial-mesenchymal transition (EMT) and cancer progression (28,29).

Despite growing evidence of circRNA involvement in oncogenesis, the relationship between circRNAs and CCa remains underexplored. Most studies address circRNAs and alternative splicing separately, lacking integration of their combined roles (30,31). The present review focuses on the interplay between SFs and circRNAs in the context of CCa pathogenesis; to support this, a literature review was conducted using PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.elsevier.com/products/scopus/search) and Google Scholar: (https://scholar.google.com/). Search terms included 'circular RNA', 'splicing factors', 'alternative splicing', 'cervical cancer', 'HPV oncogenesis', 'ceRNA network' and combinations thereof. Studies published between 2006 and 2024 that provided mechanistic, diagnostic or regulatory insights relevant to circRNAs or SFs were included. Articles unrelated to cancer, lacking original data or not peer-reviewed were excluded. Relevant findings were qualitatively synthesized, focusing on emerging patterns, molecular interactions and translational potential.

2. Epidemiology

In sub-Saharan Africa, CCa is a major health concern, ranking as the second most prevalent cancer and the leading cause of cancer-related mortality among women (32). Over the past three decades, CCa incidence among young women has notably increased, with current rates ranging from 10 to 40% (33). According to GLOBOCAN 2022, ~348,189 women died from CCa globally (2), reflecting a rise in mortality compared with 2020. In Africa alone, an estimated 80,000 women are diagnosed annually, with >50,000 (~70%) succumbing to the disease (34). Despite its high incidence and poor prognosis, CCa remains preventable and treatable when detected early. Among women co-infected with HIV, the average age at diagnosis is 10-15 years younger than the general population (35).

The impact of CCa is underscored by the wide disparities in mortality between high-income and LMICs (Fig. 1). In 2018, there were an estimated 570,000 cases of CCa and 311,000 CCa-associated deaths globally, with LMICs accounting for ~90% of deaths (5,36). The World Health Organization later reported 660,000 new cases and 350,000 deaths in 2022, again with 90% occurring in LMICs (37). Incidence and mortality rates vary considerably across regions, with the Caribbean, Latin America and sub-Saharan Africa reporting the highest burdens (4). These elevated rates are largely attributable to limited access to screening and treatment, a high prevalence of HPV infection and other region-specific risk factors (38). By contrast, high-income countries have reduced CCa incidence and mortality through widespread screening and HPV vaccination (39).

Addressing the burden of CCa in LMICs requires acknowledging the challenges to implementing effective management measures (40). In sub-Saharan Africa, critical healthcare infrastructure for early detection and advanced disease management is often lacking. Even when services are available, cultural barriers, including stigma, traditional beliefs and religious practices, may limit women's access to essential care (4,40,41). Fig. 1 shows the worldwide burden of CCa, highlighting potential regional disparities.

3. Pathophysiology of CCa

Although various genetic and epigenetic changes contribute to the initiation of CCa, persistent HPV infection is the primary driver of disease progression (42). Prolonged HPV infection leads to the upregulation of viral oncogenes, resulting in molecular disruptions in cervical epithelial cells (43). HPV-encoded oncoproteins, particularly E5, E6 and E7, drive oncogenic transformation (8) by suppressing tumor suppressor proteins such as p53 and retinoblastoma protein, while interfering with key signaling pathways that regulate genomic stability and the cell cycle (44,45). E5 further promotes oncogenesis by upregulating factors such as epidermal growth factor receptor and cellular mesenchymal-epithelial transition, both of which enhance HPV-related gene expression. As these molecular changes accumulate, the risk of malignant transformation increases (46,47).

HPV-driven cervical carcinogenesis typically unfolds in four stages, as illustrated in Fig. 2. The initial stage involves infection of basal epithelial cells, often through microabrasions, followed by immune clearance in most cases. However, in ~10% of individuals, the infection persists and leads to the development of low-grade squamous intraepithelial lesions,

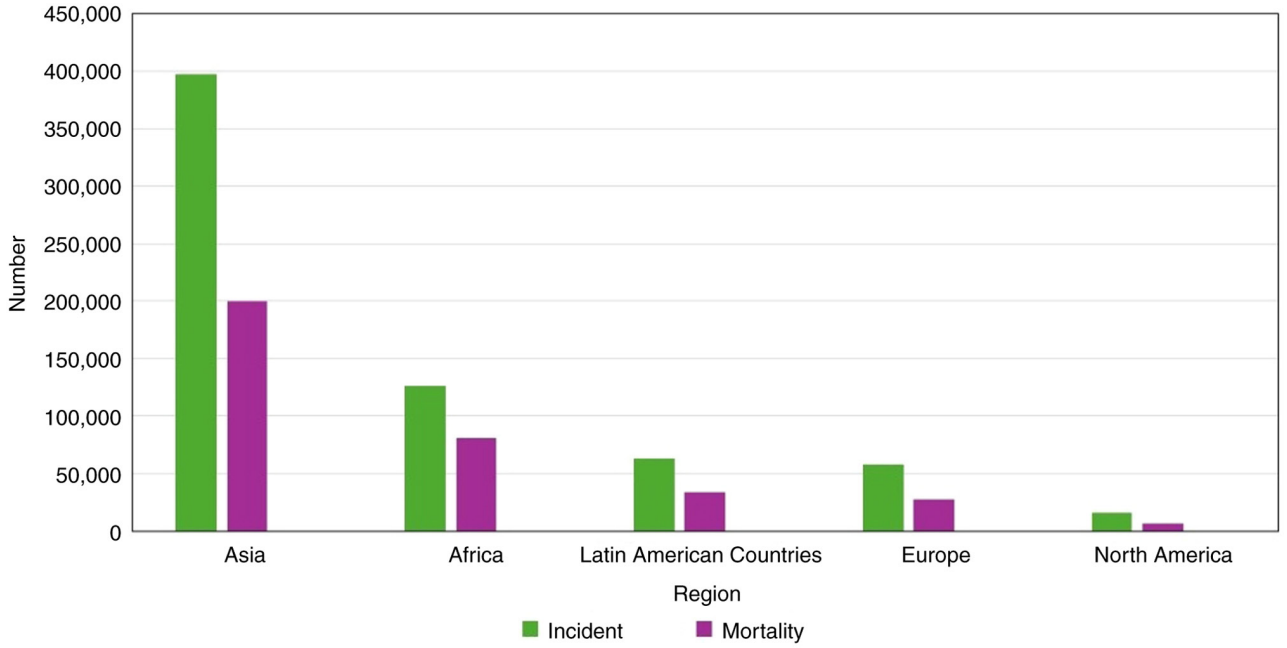

Figure 1. Incidence and mortality rates of cervical cancer across continents in 2022 based on the most recent projection of worldwide cancer burden from the International Agency for Research on Cancer (118).

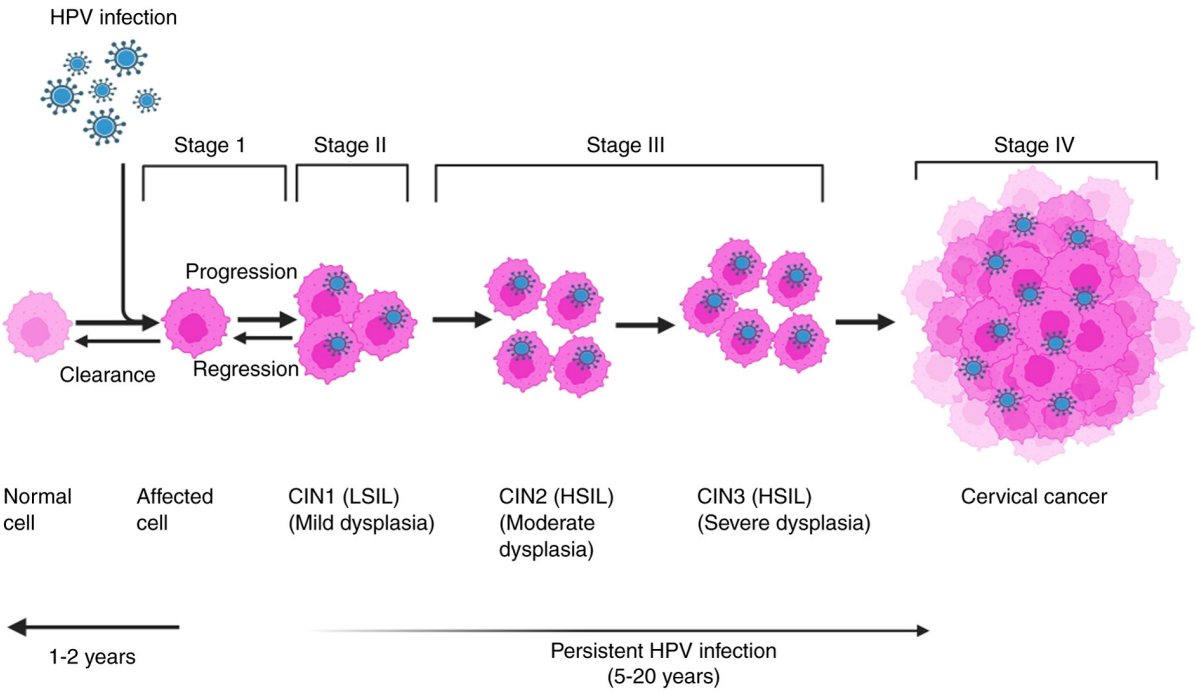

Figure 2. HPV-induced cervical carcinogenesis. HPV primarily infects the basal layer of the cervical epithelium, which is exposed by abrasion. Most infections are eliminated by the immune system within 1-2 years, but chronic infections may cause disease progression. CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

classified as cervical intraepithelial neoplasia grade 1 (CIN1). CIN1 lesions may progress to high-grade lesions (CIN2 and CIN3), which, if left untreated, can evolve into invasive carcinomas (40,48). Notably, CIN1 often regresses spontaneously, with ~60% of lesions resolving without intervention. CIN2 also shows high spontaneous regression rates, particularly among younger women, with ~63% of lesions resolving independently (49,50).

Invasive CCa is staged according to the International Federation of Gynecology and Obstetrics (FIGO) system (51), which ranges from stage I (cancer confined to the cervix) to stage IV (distant metastasis involving organs such as the liver and lungs) (7,52,53). Treatment strategies are determined by the clinical stage (54). Early-stage CCa is typically managed with surgery and radiation therapy (55), whereas advanced stages require chemoradiation (56,57), often using platinum-based

regimens (56,58). For late-stage or metastatic disease, systemic therapies and radiotherapy are commonly employed, including in LMICs (40,58). However, treatment efficacy in these regions is frequently compromised by inadequate infrastructure, limited numbers of trained professionals and the high costs associated with surgical care (40,58).

4. Regulation of circRNA cyclization and biogenesis by SFs

circRNAs are primarily generated through the back-splicing of pre-mRNA at canonical splice sites, a process regulated by SFs (59). Canonical pre-mRNA splicing and exon cyclization are mutually exclusive, with this competition serving as a conserved, tissue-specific mechanism in animals (60).

One well-characterized example is circMbl, derived from the mannan-binding lectin (MBL) gene; the biosynthesis of circMbl is tightly regulated by the MBL protein, which binds to conserved motifs in the flanking introns, promoting circRNA formation (60). Similarly, Src-associated mitosis of 68 kDa (SAM68) has been shown to promote circRNA production *in vivo* and *in vitro* by interacting with Alu elements in SMN pre-mRNA (61). This interaction represents a unique regulatory mechanism linking SAM68 and Alu elements in circRNA biogenesis. Another SF, SF proline/glutamine-rich (SFPQ), is enriched in introns flanking Distal-Alu-Long-Intron (DALI) circRNAs, which are characterized by long introns and distal inverted Alu elements. Depletion of SFPQ markedly reduces DALI circRNA expression (62), underscoring the essential role of SFs in tissue-specific circRNA regulation.

The regulatory function of SFs in circRNA biogenesis has been observed in various types of cancer. In hepatocellular carcinoma, circRNA levels are reduced; suppression of nudix hydrolase 21 increases circRNA production and promotes the formation of UGUA motifs (63). In oral squamous cell carcinoma, circUHRF1 inhibits microRNA (miRNA/miR)-526b-5p, leading to increased expression of c-Myc, which in turn activates transforming growth factor β1 and epithelial splicing regulatory protein 1 (ESRP1) transcription. ESRP1 then accelerates circUHRF1 cyclization, forming a regulatory feedback loop (64).

In glioma, SRSF10 regulates circATXN1 production by binding to flanking Alu elements; knockdown of SRSF10 markedly decreases circATXN1 levels (65). In addition, it has been shown that ~40% of expressed genes in human B-lymphoid cells produce circRNAs, implicating alternative back-splicing and the involvement of RNA-binding proteins, particularly SFs such as SRSF3, in exon circularization and circRNA formation (66). Despite these insights across various malignancies, the role of SFs in circRNA regulation in CCa remains largely unexplored.

5. circRNAs in cancer pathogenesis

circRNAs are a class of ncRNAs generated through head-to-tail splicing of exons, resulting in covalently closed loops lacking 5' caps or 3' polyadenylated tails (67). These molecules contribute to cancer progression via several key mechanisms (68) as shown in Fig. 3. Firstly, circRNAs act as sponges for miRNAs, limiting their ability to bind mRNA targets and regulate gene expression (69). Second, circRNAs can function as decoys for proteins, such as RNA-binding proteins, to regulate their functions (70). Third, circRNAs modulate gene transcription and alternative splicing through RNA-RNA interactions (71). These properties render circRNAs potential markers for cancer diagnosis and treatment.

circRNA mechanisms in CCa pathogenesis. circRNAs are differentially expressed in CCa tissues compared with healthy tissues, suggesting their role in tumorigenesis (8,72). Abnormally expressed circRNAs are considered to promote tumor formation by acting as miRNA sponges (73). The roles of miRNAs in cancer, including CCa, have been widely studied, revealing that their expression depends on cellular context and the availability of mRNA targets. In some cases, miRNAs are downregulated and act as tumor suppressors, while in others, they are upregulated and function as oncogenes, promoting aggressive cancer phenotypes. This duality underscores the pleiotropic nature of miRNAs in cancer biology. For example, the miR-584 family has been implicated in multiple types of cancer and can influence distinct signaling pathways depending on the tissue type and subcellular localization (74).

Tumor-promoting circRNAs are typically upregulated in CCa and are associated with poor prognosis. For example, hsa_circ_0141539 is more abundant in CCa tissues than in adjacent healthy tissues, and is associated with tumor size, FIGO stage and myometrial invasion. hsa-circ-0141539 functions as a sponge for miR-518d-5p/519-5p, upregulating the chromobox 8 gene, which contributes to tumorigenesis in cervical cells (75). Hsa_circ_0141539 also sponges miR-506, leading to increased expression of the snail family transcriptional repressor 2, a direct target of miR-506; silencing hsa_circ_0141539 has shown therapeutic promise for CCa (76).

Other oncogenic circRNAs include hsa_circRNA_101996, which sponges miR-8075 to promote the expression of the targeting protein for xklp2. circ-EIF4G2 also affects CCa cell malignancy via the miR-218/HOXA1 pathway (77,78). Another circRNA, hsa_circ_0001038, is upregulated in CCa cell lines compared with in healthy cells, where it promotes proliferation, migration and invasion, and is derived from the DNA-directed RNA polymerase I subunit RPA1 gene and is 193 base pairs long. In addition, circRNA_400029 and circEPSTI1 inhibit apoptosis via the miR-1285-3p/TLN1 and miR-375/409-3P/515-5p-SLC7A11 pathways, respectively (40).

circSLC26A4 serves a role in the progression of CCa by regulating the miR-1287-5p/HOXA7 axis (40). Furthermore, hsa_circ_0023404, which is markedly upregulated in CCa tissues, advances CCa progression by sponging miR-136 and activating the TFCP2/YAP signaling axis. circ_0003221 is also upregulated in CCa, and its knockdown hinders cell migration, proliferation, invasion and EMT while inducing cell cycle arrest. This circRNA sponges miR-758-3p, leading to the increased expression of cytoplasmic polyadenylation element-binding protein 4 (CPEB4), which is directly targeted by miR-758-3p; silencing circ_0003221 has been revealed to suppress CCa progression through the miR-758-3p/CPEB4 axis (79). Additionally, circEPSTI1, which is notably upregulated in CCa, regulates ferroptosis through the circEPSTI1-miR-375/409-3P/515-5p-SLC7A11 axis, influencing CCa cell proliferation through competing endogenous RNA

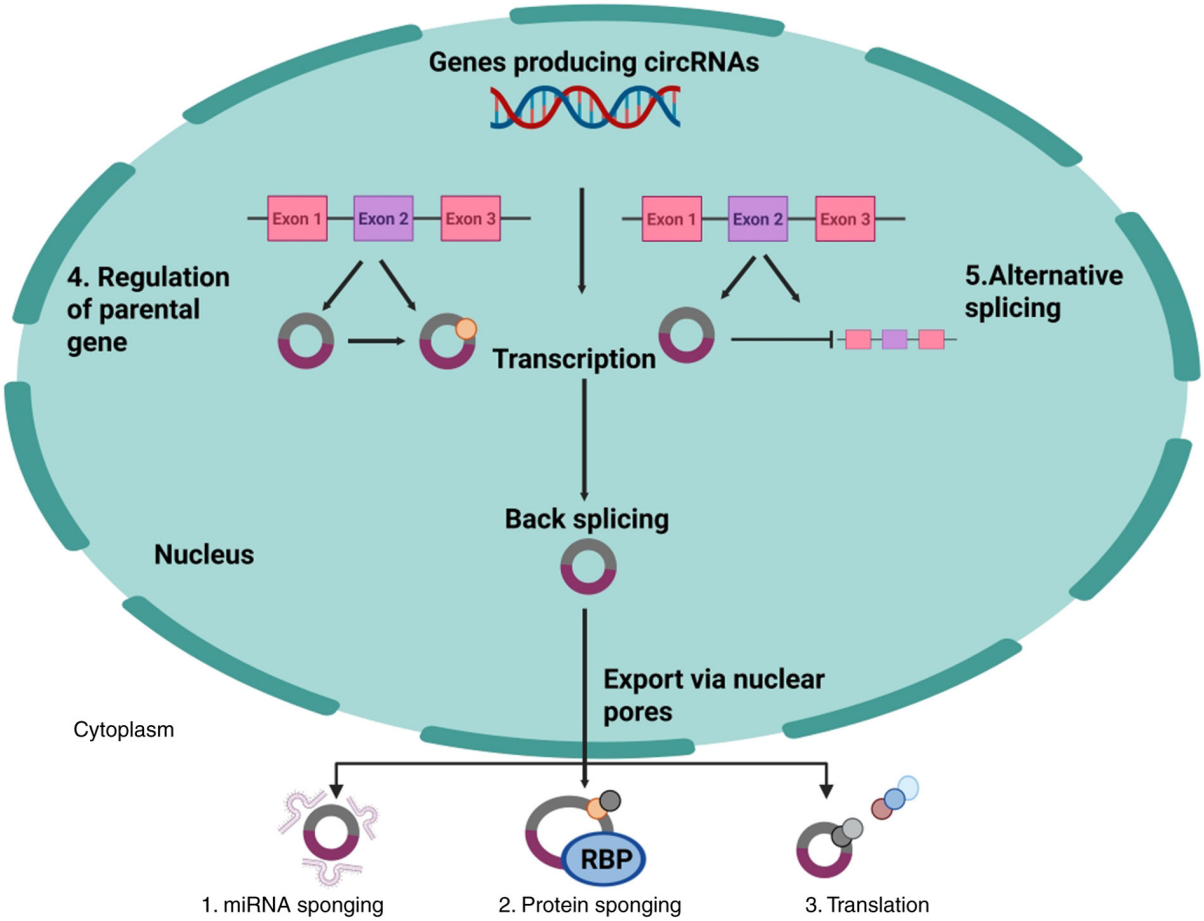

Figure 3. circRNA biogenesis and cancer mechanisms. circRNAs are transcribed by RNA polymerase II and generated through back-splicing. They are typically transported to the cytoplasm and contribute to cancer through several mechanisms: i) Acting as miRNA or ii) protein sponges, iii) being translated into proteins, iv) competing with linear RNAs for splicing, and v) modulate gene transcription and alternative splicing through RNA-RNA interactions. circRNA, circular RNA; miRNA, microRNA; RBP, RNA-binding protein.

mechanisms, presenting as a potential biomarker and treatment target. circ_0005576, which is upregulated in CCa samples and cells, enhances CCa cell proliferation and mobility by sponging miR-153-3p; the circ_0005576/miR-153-3p/KIF20A pathway offers a promising therapeutic target for CCa (80). Several other circRNAs involved in CCa pathogenesis are summarized in Table I.

circRNAs as potential markers in CCa: Screening diagnosis. Due to their high tissue specificity and resistance to exonuclease degradation, circRNAs exhibit notable structural stability (70), making them ideal candidates for non-invasive diagnostic biomarkers (81). They can be detected in blood, saliva and urine, enabling liquid biopsy applications. circRNAs are also linked to key clinical parameters in CCa, such as metastasis, age, sex and Tumor-Node-Metastasis stage (70,82). A previous RNA sequencing study identified ~80,000 circRNAs in cervical tissues, with ~25,000 showing differential expression. Furthermore, ~18,000 circRNAs were detected in cell-free plasma samples, and ~2,700 showed altered expression following surgical tumor removal (83). These findings reinforce the diagnostic potential of circRNA expression in CCa, with expression profiles clearly distinguishing tumor from normal tissues (84). Some notable examples include circRNA8924 (85), circ-ATP8A2 (86) and circ-0000745 (87), which have been shown to be upregulated in cervical cancer and promote cancer progression. Additionally, hsa_circ_0018289 (88), circRNA-000284, hsa_circ_0023404 (89) and circ_0067934 have also been identified as being upregulated in cervical cancer and involved in its progression (90).

circRNAs as prognostic biomarkers in CCa. circRNAs are increasingly associated with clinical prognostic indicators such as tumor size, disease stage and metastasis. Given the limitations of existing therapies and high recurrence rates, reliable biomarkers for disease progression and relapse are urgently needed. Previous studies have supported the utility of circRNAs as prognostic markers (91), including for tumor recurrence (92). For example, reverse transcription-quantitative polymerase chain reaction has revealed that low serum levels of circFoxO3a are associated with poor prognosis in patients with squamous CCa (93). Similarly, elevated circEIF4G2 expression is associated with larger tumor size, lymph node involvement and reduced patient survival (78). These findings underscore the potential of circRNAs to guide prognosis, although the mechanisms underlying their dysregulation remain incompletely understood.

Table I. circRNAs in CCa pathogenesis.

First author/s, year	circRNA	Expression level	Regulatory axis	Oncogenic role in CCa	Effect on CCa	(Refs.)
Zhang *et al*, 2018	hsa_circ_0023404	Upregulated	miR-136/TFCP2	Oncogenic	Facilitates CCa development and progression	(81)
Gu *et al*, 2020	circ_0003221	Upregulated	miR-758-3p/ CPEB4	Oncogenic	Contributes to CCa progression	(82)
Xie *et al*, 2021	circ-EIF4G2	Upregulated	miR-218/HOXA1	Oncogenic	Enhances cell proliferation, migration, invasion and colony formation	(79)
Zhang and Xin, 2018	circ-ITCH	Down regulated	miR-93-5p/FOXK2	Tumor suppressor	Inhibits cell proliferation, migration and invasion	(85)
Ma *et al*, 2019	hsa_circ_0001038	Upregulated	miR-337-3p/ CNNM3	Oncogenic	Promotes cell proliferation, migration and invasion	(80)
Wei *et al*, 2021	circRNA_400029	Upregulated	miR-1285-3p/ TLN1	Oncogenic	Promotes cancer proliferation and invasion, and inhibits apoptosis	(86)
Tang *et al*, 2020	circEPSTI1	Upregulated	miR-375/409-3P/ 515-5p-SLC7A11	Oncogenic	Stimulates cancer growth and invasion, inhibits cell death	(87)
Li *et al*, 2019	circ0001955	Upregulated	miR-188-3p/ NCAPG2	Oncogenic	Promotes tumorigenesis and metastasis in CCa	(83)
Tang *et al*, 2019	hsa_circ_0000263	Upregulated	miR-150-5p/ MDM4/p53	Oncogenic	Promotes cell proliferation, migration and cell cycle regulation	(88)
Yi *et al*, 2019	hsa_circ_0000301	Upregulated	miR-1228-3p/ IRF4	Oncogenic	Promotes cancer progression	(89)
Zhang *et al*, 2018	hsa_circRNA_101996	Upregulated	miR-8075/TPX2	Oncogenic	Promotes cell proliferation and invasion	(78)
Marima *et al*, 2021	circCLK3	Upregulated	miR-320a/ Fox M1	Oncogenic	Promotes CCa progression	(41)
Chen *et al*, 2023	circ_0084927	Upregulated	miR-142-3p/ ARL2	Oncogenic	Promotes CCa development	(90)
Zheng *et al*, 2018	circRNA_000284	Upregulated	miR-506/Snail-2	Oncogenic	Promotes cell proliferation and invasion in CCa	(91)
Zhao *et al*, 2019	hsa_circ_0000515	Upregulated	miR-326/ELK1	Oncogenic	Promotes CCa progression	(92)

CCa, cervical cancer; circRNA, circular RNA; miR, microRNA.

circRNAs as therapeutic targets for CCa. Dysregulated circRNAs also represent potential therapeutic targets. For example, hsa_circ_0000515 is upregulated in CCa tissues, and promotes tumor growth, migration and invasion. By contrast, downregulation of hsa_circ_0000515 suppresses cell proliferation, and induces apoptosis and autophagy (94). Several other circRNAs, including hsa_circRNA_000596, hsa_circRNA_104315, hsa_circRNA_400068, hsa_circRNA_101958 and hsa_circRNA_103519, form part of a circRNA-miRNA-mRNA network targeting ribonucleotide reductase M2, influencing responses to chemotherapy via mRNA variants such as rs5030743 and rs1130609 (95). Additionally, circ_0104541 is upregulated in CCa compared with in precancerous tissues, and its silencing reduces cell migration and invasion. These findings reinforce the therapeutic relevance of targeting circRNAs in CCa (80,96).

6. circRNAs as modulators of HPV infection in CCa

CCa is closely linked to persistent HPV infection, particularly HPV16 and HPV18. The viral oncoproteins E6 and E7 drive the transformation of cervical epithelial cells and considerably contribute to the pathogenesis of CCa (97). Research has shown that oncogenic HPV strains can generate their own circRNAs.

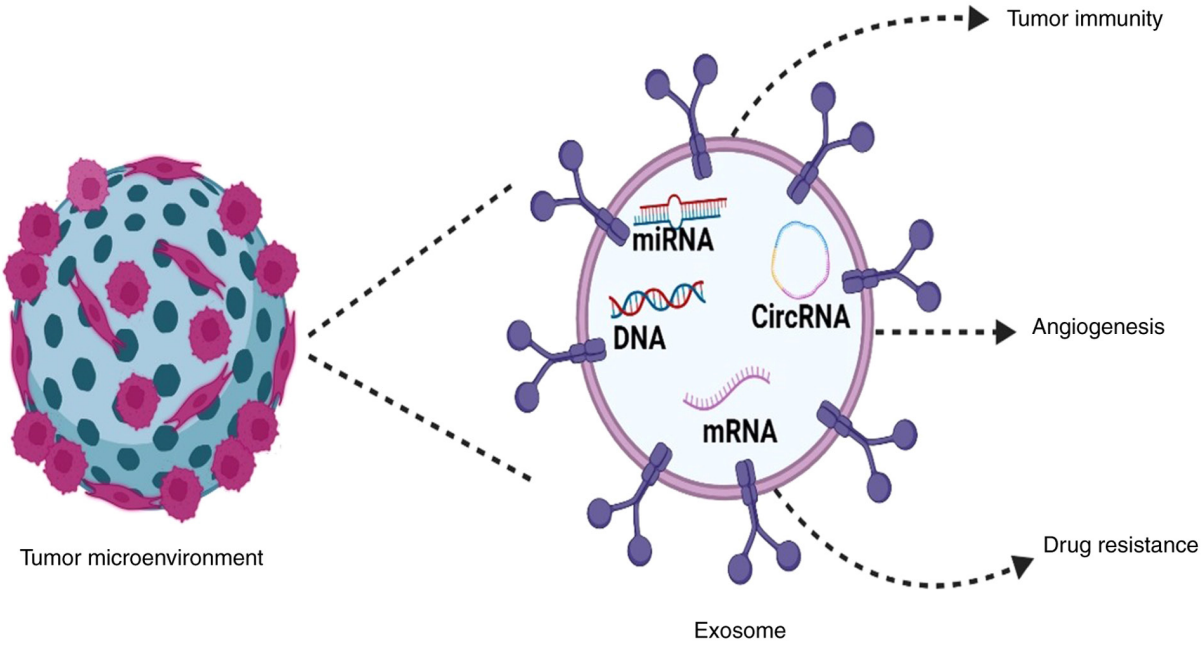

Figure 4. Roles of exosomal circRNAs in the tumor microenvironment. Exosomal circRNAs from donor cells influence interactions with recipient cells both locally and distantly, affecting cancer progression through modulation of drug resistance, angiogenesis, immunity, epithelial-mesenchymal transition, metabolism, invasion and metastasis. circRNA, circular RNA; miRNA, microRNA.

One such molecule, circE7, contains the E7 oncogene and has been identified in HPV16-infected cells. circE7 is found in the cytoplasm, is associated with polysomes, and exhibits N6-methyladenosine (m6A) modification. Notably, circE7 serves as a template for the E7 oncoprotein, and disrupting circE7 reduces E7 protein levels, limiting malignant transformation in HPV16-positive CCa cells such as CaSki (98). *In vivo*, circE7 suppression can inhibit tumor formation in xenograft models. Moreover, data from The Cancer Genome Atlas confirmed that circE7 is expressed in HPV-positive tumors, supporting the functional relevance of virus-derived circRNAs in cancer development (98).

Further research on circRNA expression profiles in CaSki cells has identified 526 dysregulated circRNAs following E7 expression, including 352 upregulated and 174 downregulated circRNAs (97,99-101). A number of these circRNAs are involved in cancer-related pathways, such as the mammalian target of rapamycin signaling pathway (102,103). Notably, higher circE7 expression in HPV16-positive tumors has been associated with improved overall survival, suggesting its potential as a prognostic biomarker. Although the understanding of virus-host circRNA interactions remains limited, evidence suggests that viruses may exploit circRNA biogenesis to facilitate oncogenesis and progression (71,104-106).

7. Exosomal circRNAs in the CCa tumor microenvironment

Exosomes are extracellular vesicles that mediate intercellular communication by transferring biomolecules such as proteins, lipids and RNAs, including circRNAs. In cancer, exosomal circRNAs are increasingly recognized for their roles in modulating key processes in the tumor microenvironment (TME) (107), including drug resistance, angiogenesis, tumor immunity, EMT, metabolism, invasion and metastasis (Fig. 4) (108). Notably, circ_PVT1 has been identified as an oncogenic exosomal circRNA upregulated in CCa (109). Silencing circ_PVT1 suppresses CCa cell migration and invasion, and may prevent lung metastasis (109). Conversely, elevated circ_PVT1 expression enhances metastatic potential by promoting EMT through the miR-1286 axis, establishing circ_PVT1 as a potential therapeutic target (110).

Similarly, circ-HIPK3 is highly expressed in CCa tissues and exosomes, whereas silencing circ-HIPK3 impairs cell proliferation and induces apoptosis. circ-HIPK3 functions by sponging miR-338-3p, leading to upregulation of hypoxia-inducible factor-1α, which supports tumor progression (111). Furthermore, circSYT15 contributes to cisplatin (DDP) resistance; circSYT15 is upregulated in DDP-resistant CCa cells and exosomes, where it promotes resistance via the miR-503-5p/RSF1 axis (96). These findings highlight the critical role of exosomal circRNAs in regulating cell communication in the TME, and reveal their potential as biomarkers and therapeutic targets in combating metastasis and treatment resistance.

8. circRNAs and epigenetic mechanisms in CCa

Epigenetics involves heritable changes in gene regulation that do not alter the underlying DNA sequence (112,113). These modifications include histone modification, DNA methylation, chromatin remodeling and regulation by ncRNA (114). Together, these mechanisms ensure precise control of gene expression and are critical for normal development and cell differentiation. Dysregulation of epigenetic mechanisms is implicated in various diseases, particularly cancer.

circRNAs, like other ncRNAs, can influence epigenetic regulation at the transcriptional level (112,115). Aberrant circRNA expression has been observed in CCa, suggesting a functional role in tumor progression (116). For example,

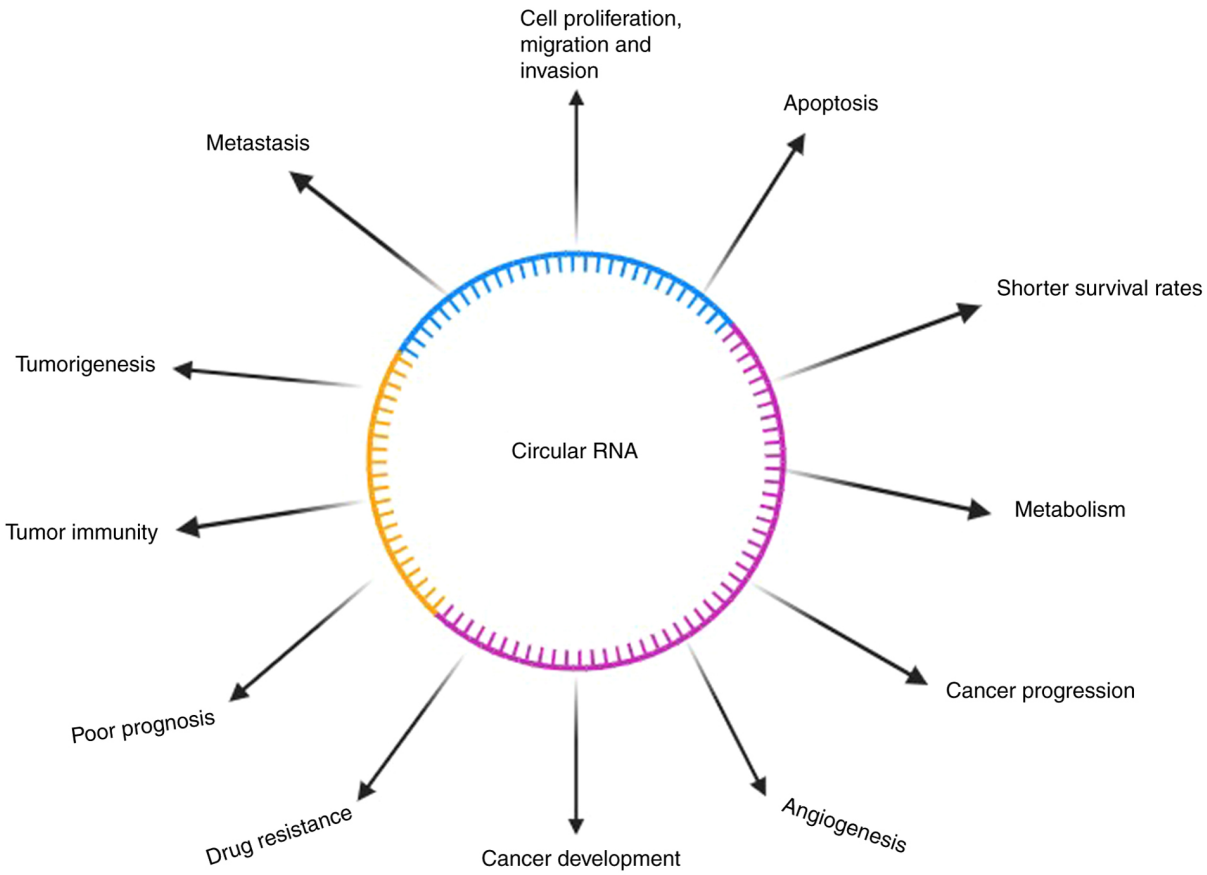

Figure 5. Overview of circular RNA involvement in cancer.

circE7, derived from HPV16, encodes the E7 oncoprotein independently of its linear RNA counterpart. The translation of E7 is influenced by m6A modification, a key epigenetic marker. Knockdown of RNA methyltransferases METTL3 and METTL14 notably reduces circE7 expression and E7 protein levels, while mutations in m6A consensus sites within the 5' untranslated region of circE7 also impair its expression, Notably, specific disruption of circE7 in CaSki CCa cells reduces E7 protein levels and inhibits CCa cell growth both *in vitro* and in tumor xenografts. This demonstrates that circE7 is essential for the transformed growth of these cells, and consequently, impaired circE7 expression inhibits CCa progression (98). Notably, these effects do not influence the levels of linear RNA, indicating that m6A modification specifically enhances circE7 stability and translation. Additionally, circ0000069 promotes CCa cell proliferation and migration by sponging miR-4426; the expression of circ0000069 is also regulated by m6A modification, as METTL3 knockdown reduces both m6A levels and circ0000069 expression, suggesting that m6A enhances the stability of circ0000069 (117).

9. Challenges to the potential diagnostic and prognostic roles of circRNAs in CCa

Unlike linear RNAs, circRNAs possess a closed-loop structure lacking 3' and 5' ends. This unique configuration enhances their stability and persistence in circulation, particularly within serum-derived exosomes (118). circRNAs also exhibit tissue- and cancer-type-specific differential expression, including in CCa, making them promising candidates for non-invasive diagnostic and prognostic biomarkers (113,114).

Despite this potential, several challenges hinder the clinical application of circRNAs. Notably, circRNAs need to be validated in clinical settings; most circRNA studies have been conducted on small sample sizes, often without replication or validation in larger, diverse patient cohorts (115). Furthermore, the lack of standardized nomenclature conventions for circRNAs can lead to confusion, inconsistencies across studies and difficulty in data interpretation (116). There are also technical limitations. circRNA identification and quantification are complicated by sequence overlap with host gene-derived miRNAs and the technical challenges of detecting back-splice junctions (117). These factors increase the risk of experimental artefacts and data variability. While numerous circRNAs have been implicated in cancer biology, the precise molecular mechanisms through which they exert oncogenic or tumor-suppressive effects in CCa remain poorly characterized.

To overcome these limitations, large-scale, multi-center studies are essential for validating circRNA expression patterns and establishing their clinical relevance. Standard protocols for naming, validating and quantifying circRNAs must be established to facilitate the comparability of results across studies. Further investigation into the functional roles and regulatory mechanisms of circRNAs in CCa will be critical to realizing their full potential as diagnostic tools and therapeutic targets (113).

10. Conclusions

The regulation of circRNA cyclization and biogenesis by SFs represents a complex and dynamic process that influences multiple cellular functions, including tumor progression. SFs such as MBL, SAM68 and SFPQ serve pivotal roles in circRNA formation by modulating the balance between canonical pre-mRNA splicing and back-splicing. These regulatory interactions underscore the intricate molecular framework governing circRNA formation. Dysregulation of circRNAs has been implicated in a variety of malignancies, including CCa, highlighting their importance as biomarkers and therapeutic targets. Fig. 5 provides a conceptual summary of the mechanisms discussed throughout the present review. However, while considerable progress has been made in understanding circRNA biology, the specific interactions between SFs and circRNAs in CCa remain largely unexplored. This knowledge gap presents a compelling opportunity for future research to determine how SF-mediated circRNA regulation contributes to CCa pathogenesis and progression. Elucidating these mechanisms will enhance the understanding of CCa, which may lead to the development of novel diagnostic and therapeutic targets based on circRNA modulation in CCa.

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Authors' contributions

AN and RM prepared the original draft. RM, AB, NX, OF and ZD reviewed and edited the manuscript. RM and ZD conceptualized the study. RM and ZD acquired funding. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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