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Review Article

# The roles of non-coding RNAs in Hirschsprung's disease

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ABSTRACT

Hirschsprung's disease (HSCR) is a congenital disorder characterized by the absence of ganglion cells in the colon, leading to various intestinal complications. The etiology of HSCR stems from complex genetic and environmental interactions, of which the intricate roles of non-coding RNAs (ncRNAs) are a key area of research. However, the roles of ncRNAs in the pathogenesis of HSCR have not been fully elucidated. In order to understand the variety of symptoms caused by HSCR and develop new therapeutic approaches, it is essential to understand the underlying biological genetic basis of HSCR. This review presents a comprehensive overview of the current understanding regarding the involvement of ncRNAs in HSCR, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs). Additionally, it provides a summary of the molecular mechanisms through which ncRNAs regulate the expression of genes related to the proliferation, migration, and differentiation of intestinal neural crest cells, thereby contributing to the advancement of HSCR research.

## 1. Introduction

### 1.1. Hirschsprung's disease

Hirschsprung's disease (HSCR), also known as aganglionosis, is a congenital disorder stemming from a failed migration of intestinal neural crest cells (NCCs) to the distal intestine during the 5th to 12th weeks of embryogenesis, leading to an absence of ganglion cells in the intermuscular and submucosal plexus [1]. The incidence is approximately 1/5000, with most cases being sporadic and only 5%–20% being familial. Patients primarily present with delayed meconium expulsion and constipation. Serious complications, such as bowel perforation, hemorrhage and possibly lethal colitis, may occur if the disease is not promptly managed [2].

As a genetic and environmentally related disease [3]. Over 20 genes have been linked to HSCR's onset, with the RET/GFRA1/GDNF and ECE1/END3/ENDRB signaling cascades being predominantly involved [4,5]. Other associated genes include transcription factors like SOX10, PHOX2B, ZFHX1B; the cell adhesion molecule L1CAM; signaling proteins like SEMA3A, SEMA3C, SEMA3D; neurotrophic elements such as NRTN, ARTN, PSPN, NTF3 (with NTRK as its ligand); Hedgehog signals like GLI1, SHH, IHH; and neuregulins like NRG1, NRG3 [6–8]. Though these genes significantly influence HSCR's development, they don't fully clarify the enteric nervous system's (ENS) aberrant development. A schematic representation of these genes is provided in Fig. 1.

Epigenetics regulates gene expression without involving changes in gene sequence. Studies have shown that various epigenetic modifications such as histone modification, RNA methylation, DNA methylation, and non-coding RNAs (ncRNAs), modulate the expression of genes associated with the pathogenesis of HSCR [9]. NcRNAs are a class of RNA molecules that are not engaged in protein encoding, and act as a key post-transcriptional regulator that can affect the expression of downstream mRNA, and thus participates in a variety of biological processes, including cell growth, apoptosis, differentiation, and immune responses [10,11]. Currently, ncRNAs have been found to be implicated in several neurological disorders such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Peripheral nerve injury, and Neuroblastoma [12–14]. Many studies have also found that ncRNAs can regulate the expression of genes related to NCCs migration, proliferation and differentiation [15–17]. In this review, we summarize the action of ncRNAs in the pathogenesis of HSCR and deepen our understanding of the pathogenesis of HSCR.

### 1.2. Non-coding RNA

Non-coding RNAs represent a vast class of transcripts generated post DNA transcription. Beyond transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), this group also encompasses regulatory ncRNAs, which may

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undergo specific epigenetic modifications [18]. Regulatory ncRNAs are categorized by their nucleotide (nt) length into small non-coding RNAs (length <200 nt) and long non-coding RNAs (length >200 nt). Among small non-coding RNAs, we find several types: microRNAs (miRNAs), which mature through the actions of enzymes like DGCR8, DICER, and DROSHA and typically span 22-24 nt; Small interfering RNAs (siRNAs), double-stranded entities that specifically target messenger RNAs (mRNAs) and measure around 20-24 nt; and piwi-interacting RNAs (piRNAs), originating from single-stranded mini-gene precursors, which guide PIWI proteins to influence target mRNAs expression, with lengths generally between 24-31 nt. Long non-coding RNAs (lncRNAs) can be further classified based on their genomic positioning in relation to protein-coding genes. The categories include promoter-associated transcripts, sense, intronic, bidirectional, antisense, 3′-UTR associated transcripts, and intergenic types. Additionally, circRNAs are unique because they lack both a 5′ cap and a 3′ poly(A) tail, forming a circular structure [19–21]. NcRNAs play pivotal roles in a host of physiological functions, including gene regulation, chromatin remodeling, epigenetic modifications, RNA splicing, translation, and protein transportation [22]. The action mechanisms are varied. For instance, miRNAs typically

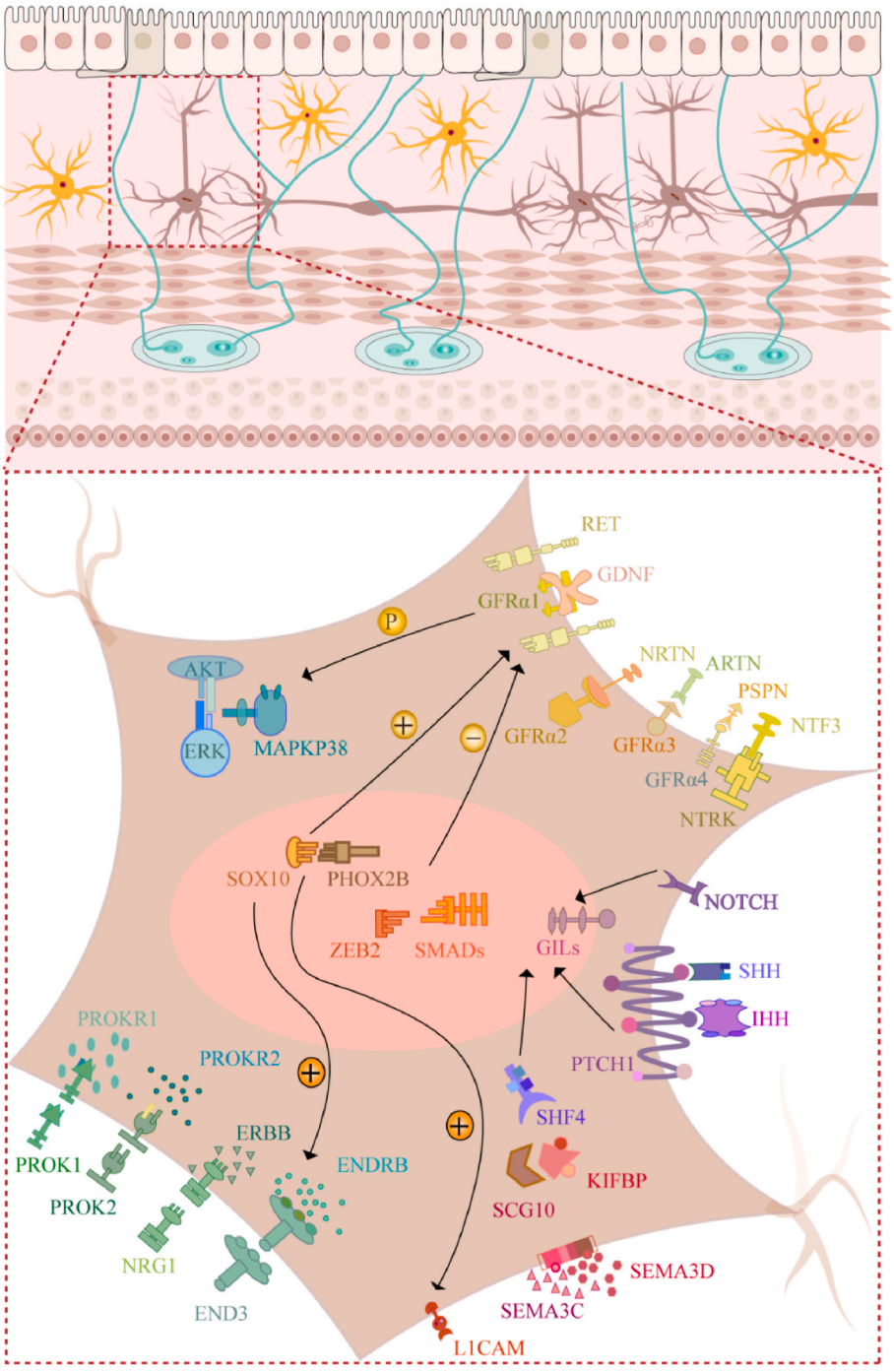


**Fig. 1.** Various intracellular signaling molecules and pathways involved in HSCR. Including receptors like RET, ENDRB; signaling proteins such as AKT, ERK; and transcription factors like SOX10, PHOX2B. Neurotrophic factors such as GDNF, ARTN, PSPN, and NTF3 interact with corresponding receptors GFRα1-4 and NTRK. Additionally, pathways like the NOTCH signaling pathway, Sonic Hedgehog (SHH) pathway, as well as other molecules (such as SEMA3C and SEMA3D), play significant roles in enteric neurons.

regulate downstream mRNAs in two principal ways: one method is by binding to the ORF region of mRNAs, forming a double-stranded structure leading to mRNA degradation; another method is by binding to the 3′-untranslated region (3′-UTR) of mRNAs, inhibiting post-transcriptional translation of mRNAs [23]. LncRNAs exert control over gene expression through multiple tiers. On the epigenetic front, lncRNAs aid in directing chromatin remodeling complexes to particular sites, leading to the subsequent silencing of linked genes. In the realm of transcriptional control, the expression of certain lncRNAs can disrupt that of nearby genes. They can also obstruct gene expression by blocking promoter regions. Moreover, lncRNAs can bind with RNA-binding proteins, steering them towards gene promoter zones to adjust gene expression. These lncRNAs further modulate transcription factor activities, and by influencing basic transcription factors, they oversee gene expression. In terms of post-transcriptional control, lncRNAs impact gene expression by pairing with mRNAs after transcription [20]. Shifting focus to circRNAs, the primary mechanisms of circRNAs function include: serving as competitive endogenous RNA; modulating selective splicing or translation; regulating the expression of parent genes; and performing biological functions through protein interactions [24]. Subsequently, this article primarily focuses on the regulatory ncRNAs linked to HSCR, zooming in on the recent developments concerning miRNAs, lncRNAs, and circRNAs. The formation process and related biological functions of ncRNAs are shown in Fig. 2.

## 2. Non-coding RNA classes associated with HSCR

### 2.1. MiRNA

MicroRNAs are a subset of small non-coding RNAs 22–24 nucleotides in length. They act as key post-transcriptional regulators, leading to mRNAs degradation or translation inhibition by binding to the 3′-UTR of

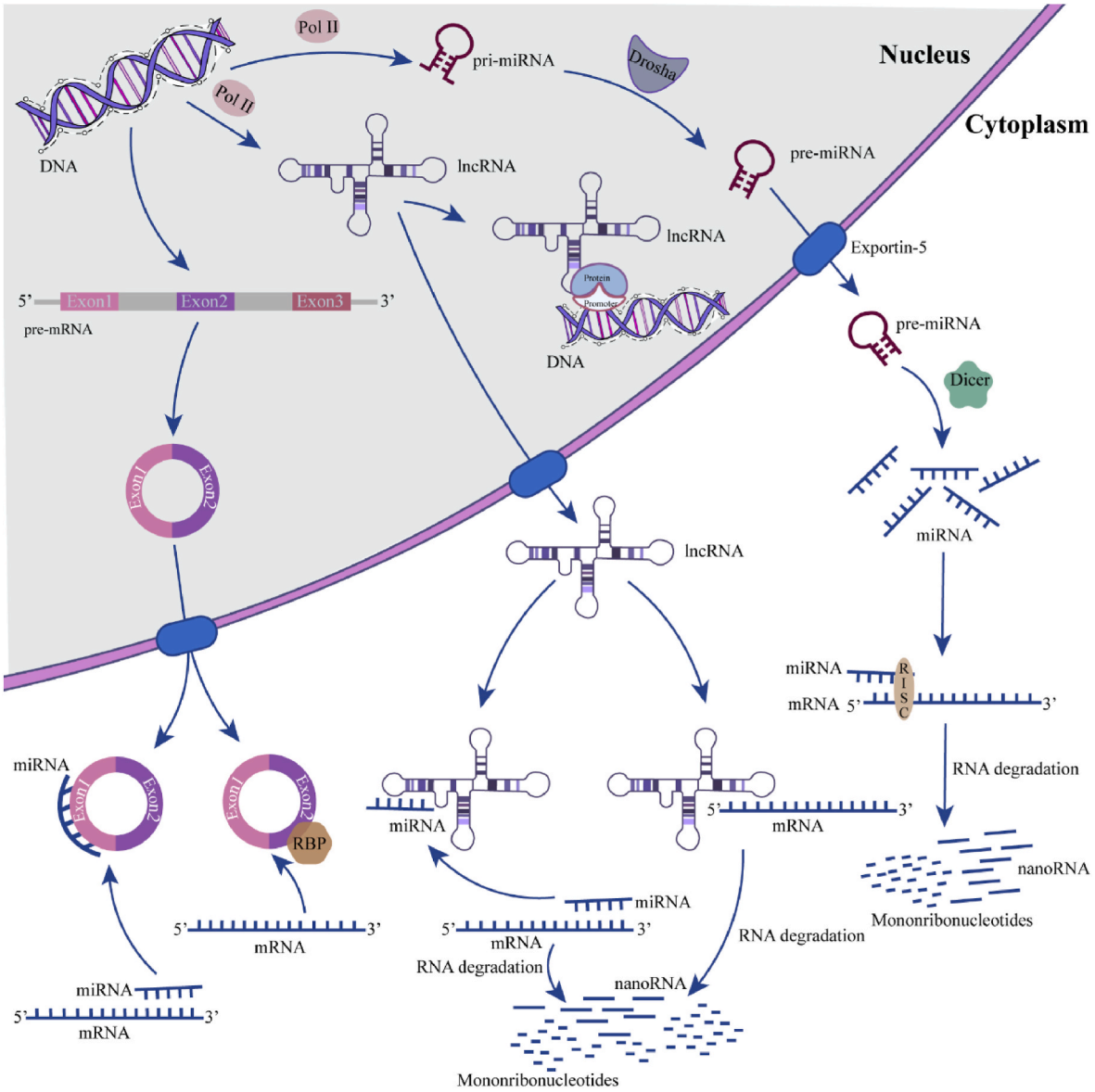


**Fig. 2.** The formation process and related biological functions of ncRNAs. DNA transcription results in primary microRNA (pri-miRNA), long non-coding RNA (lncRNA), and precursor messenger RNA (pre-mRNA). Pri-miRNA is cleaved by Drosha enzyme to form precursor miRNA (pre-miRNA), which is transported by Exportin-5. Dicer enzyme processes pre-miRNA into mature miRNA, promoting the loading of RNA-induced silencing complex (RISC) for targeted mRNA silencing. In the nucleus, lncRNA binds to gene promoter regions, promoting transcription. In the cytoplasm, lncRNA can bind with miRNA and mRNA to exert its function. Eventually degraded into monoribonucleotides. Pre-mRNA undergoes splicing, resulting in coding regions (exons) shown in purple to form circRNA. It regulates downstream gene expression by binding with miRNA or Ribonucleoprotein particles (RBPs).

its target mRNAs [25]. Research indicates that miRNAs and mRNAs have a multi-target relationship, forming a complex regulatory network, participating in the coordination of various biological processes, and playing an important role in the pathogenesis of HSCR [26].

Initially, miRNA-centered HSCR studies originated from the analysis of diseased tissue samples. Gene microarray technology is one of the most effective means of seeking breakthroughs. Li et al. [27] used microarray technology to detect differential miRNA expression between the diseased and normal intestinal tubes of HSCR, and identified 168 differentially expressed miRNAs (104 up-regulated and 64 down-regulated), seven miRNAs related to HSCR were further identified, with their target genes involving mechanisms like the RET signaling pathway in HSCR pathogenesis. Qian et al. identified miR-141-3p and miR-30a-3p as key miRNAs in HSCR, they target the mitogen-activated protein kinase signaling pathway in the development of HSCR [28]. In addition, many miRNAs with aberrant expression patterns in HSCR have been discovered. For example, miR-200a/141 and miR-92a have been found to regulate the migration and proliferation of intestinal NCCs by targeting genes related to the PI3K/PTEN/AKT pathway [29,30]. Wang et al. [31,32] have shown that miR-195-5p and miR-483-5p, target GFRA4, a member of the GNDF ligand family, and suppressing its expression can inhibit cell invasion and proliferation, as well as induce cell cycle arrest, apoptosis, and block differentiation. Additionally, miRNAs are involved in regulating the balance between enteric neurons and glial cell populations. Mi et al. [33] found that miR-124 and its target gene SOX9 were highly expressed in the diseased intestinal tubes, with the expression of SOX9 being closely tied to the development of glial cells. Similarly, miRNAs have also been confirmed to affect intestinal biological functions by influencing Cajal interstitial cells. Yang et al. [34] observed that extracellular signal-regulated kinase 1/2 can be activated when the colon of HSCR patients is in a dilated state, leading to the overexpression of miR-34c and the downregulation of the target gene SCF, thereby inhibiting the function of Cajal interstitial cells. Recently, Xu et al. [35] found that miR-424 can affect cell migration and proliferation by suppressing RICTOR expression, a finding confirmed in human neuroblastoma cells and embryonic intestinal explant culture models. They also discovered through single-cell transcriptomic data analysis that RICTOR is highly expressed in human and mouse intestinal neural cells, further suggesting that miR-424-mediated RICTOR regulation might be involved in the formation of HSCR. However, this study also has limitations in terms of small sample size, insufficient functional validation, lack of clinical relevance analyses and in *vivo* animal experiments, which are common in miRNA-related studies (such as miR-206 [36], miR-141 [37], and miR-195 [38]). Therefore, employing animal models to more comprehensively reveal the specific mechanisms of miRNA in the formation of HSCR from temporal and spatial aspects, and validating these findings with larger clinical samples to further explore its diagnostic and potential therapeutic value, remains a direction for future research. The specific research regarding miRNAs in HSCR is shown in Table 1.

**Table 1**
The expression and function of miRNAs in HSCR.

| MiRNA | Expression | Function | Mechanism | Ref |
|---|---|---|---|---|
| miR-199a-3p | ↑ | Inhibits migration and proliferation | Downregulates mTOR | [15] |
| miR-200a/141 | ↓ | Inhibits proliferation and migration | Upregulates PTEN | [29] |
| miR-92a | ↑ | Inhibits viability and migration but enhances cell apoptosis. | Regulates the KLF4/PI3K/AKT pathway | [30] |
| miR-195-5p | ↑ | Inhibits proliferation、invasion and cell cycle arrest, and accelerated apoptosis | Downregulates GFRA4 | [31] |
| miR-483-5p | ↑ | Inhibits migration and proliferation | Downregulates GFRA4 | [32] |
| miR-424 | ↑ | Inhibits proliferation | Downregulates RICTOR | [35] |
| miR-141 | ↓ | Inhibits *proliferation and migration* | Upregulates CD47 and CUL3 | [37] |
| miR-195 | ↑ | Inhibits *proliferation and migration* | Downregulates DIEXF | [38] |
| miR-218-1 | ↑ | Inhibits proliferation and migration | Upregulates RET and PLAG1 | [39] |
| miR-206 | ↓ | Inhibits *proliferation and migration* | Upregulates SDPR | [40] |
| miR-192/215 | ↓ | Inhibits migration and proliferation | Upregulates NID1 | [41] |
| miR-215 | ↓ | Inhibits migration and proliferation | Upregulates SIGLEC-8 | [42] |
| miR-939 | ↑ | Inhibits migration and proliferation | Downregulates LRSAM1 | [43] |
| miR-369-3p | ↑ | Inhibits migration and proliferation | Downregulates SOX4 | [44] |
| miR-483-3p | ↓ | Inhibits migration and proliferation | Upregulates FHL1 | [45] |
| miR-431-5p | ↑ | Inhibits migration and proliferation | Downregulates LRSAM1 | [46] |
| miR-214 | ↑ | Inhibits migration and proliferation | Downregulates PLAGL2 | [47] |
| miR-4516 | ↑ | Inhibits cell migration | Upregulates MAPK10 | [48] |
| miR-140-5p | ↓ | Inhibits migration and proliferation | Upregulates EGR2 | [49] |
| miR-142-3p | ↓ | Inhibits migration、proliferation and differentiation | Downregulates STAU1 | [50] |
| Let-7a miR-24-1 | ↑ | Reduces proliferation and migration | Downregulates RAC1 and RAC2 | [51] |
| miR-144 | ↓ | Inhibits migration and proliferation | Upregulates TFAP4 | [52] |

Due to the challenges in obtaining tissue specimens and the differences in miRNAs expression within them, detection through serum or body fluid specimens becomes necessary. To tackle this challenge, there has been a shift in the research paradigm away from tissue-centric studies towards utilizing a minimally invasive medium: blood. Tang et al. [53] gathered serum samples from 95 individuals with HSCR and 104 controls, and analyzed the expression levels of serum miRNAs using TaqMan Low-Density Array and Reverse Transcription Quantitative PCR techniques. Their results showed that five miRNAs (miR-25, miR-92a, miR-133a, miR-218-1 and miR-483-5p) were significantly elevated in HSCR patients, presenting a stark difference when compared to the controls. Importantly, miR-92a, miR-218-1, and miR-483-5p have been associated with the migration and proliferation of enteric neural crest cells (ENCCs) by influencing HSCR-related pathogenic genes and pathways [30,32,39]. Subsequently, using Risk Score and Receiver Operating Characteristic (ROC) curve analyses, the Area Under the Curve (AUC) for these five serum miRNA features in the training set and two validation sets were 0.895, 0.893, and 0.925 respectively, demonstrating the accuracy of these 5 miRNA profiles as diagnostic features for HSCR was 82.6%, significantly higher than the 70% of the most commonly used barium enema method for diagnosing HSCR. Hong et al. [54] highlighted that miR-192-5p, miR-200a-3p, and miR-200b-3p were not only specifically upregulated in HSCR lesion tissues but also manifested higher concentrations in plasma, silencing the expression of these miRNAs effectively reduced cell viability and migration. These insights reinforce the immense potential of serum miRNA markers in diagnosing HSCR. While these studies provide an experimental basis for HSCR diagnosis, high-quality, large-scale prospective cohort studies, and the development of simpler and quicker methods for more precise early detection was still an important direction in the future.

In addition to serum miRNAs, Lv et al. [55] studied the differential expression of plasma exosomal miRNAs in HSCR, revealing an upregulation of miRNAs such as miR-494-3p, miR-668-3p, miR-323a-3p, miR-605-3p, and miR-5701. Notably, miR-668-3p and miR-323a-3p emerged as the most effective and promising biomarker combination for early HSCR screening. Another study by Daiyue et al. [15] found that plasma exosomal miR-199-3p exhibited differential expression in HSCR patients and that modulating its expression influenced cell migration and proliferation. All these findings underscore the potential of miRNAs as diagnostic biomarkers for HSCR, offering prospects for early diagnosis or risk assessment. However, clinical research on these metrics has yet to be conducted.

Regarding genetic polymorphisms, single nucleotide polymorphism primarily refers to the DNA sequence polymorphism caused by single nucleotide variations at the genomic level, functional genetic polymorphisms of ncRNAs might be gene modifications related to human diseases [24]. Recent studies have uncovered potential links between miRNAs gene polymorphisms and HSCR susceptibility. A case-control study by Zhong et al., encompassing 1381 HSCR cases and 1457 controls, identified a significant association between the miR-938 rs2505901 T > C polymorphism and HSCR risk in Chinese children [56]. Likewise, research by Wu et al. [57] emphasized the connection of the miR-4318 rs8096901 polymorphism to HSCR risk in southern Chinese children, especially evident in short-segment HSCR cases. Subsequent research identified polymorphisms like pre-miR-146a rs2910164, miR-618 rs2682818 C > A, and miR-492 rs2289030 G > C as pivotal markers associated with HSCR susceptibility [58–60]. These revelations amplify the significance of miRNAs in understanding HSCR's genesis and progression. However, the presence of genetic polymorphism does not invariably lead to functional impairment; further investigation through cellular and animal experiments remains essential.

### 2.2. LncRNA

Long non-coding RNAs, which are RNA molecules exceeding 200 nucleotides in length and lack the capability to code proteins, play a vital role in gene expression regulation. This includes chromatin modification, transcription, and post-transcriptional processing [61]. LncRNAs can regulate gene expression in cis (affecting nearby genes) or trans (affecting genes located elsewhere in the genome). Those lncRNAs impact the development of ENCCs and contribute to the onset of HSCR deserve special attention [62].

There is growing evidence suggesting that genetic variant within lncRNAs influence HSCR susceptibility. For instance, Zheng et al. [63] observed a correlation between the lncRNA HOTTIP SNP rs3807598 C > G and HSCR risk. Xie et al. [64] further demonstrated that lncRNA HOTTIP can suppress NCCs migration and proliferation by modulating HOXA13 expression. Changes were observed in the expression of some pathogenic miRNAs in HSCR were induced by lncRNAs, the downregulation of miR-31/miR-31* in the narrowed segment of HSCR is caused by its host gene MIR31HG (also known as Loc554202), leading to elevated expression of ITIH5 and PIK3CG, and a decreased capacity for cell proliferation and migration [65]. Additionally, lncRNAs can function as competing endogenous RNAs (ceRNAs), interacting with miRNAs to alter the expression of downstream target genes. For instance, lncRNA AFAP1-AS acts as a ceRNA by enhancing miR-181a expression through competitively binding, which in turn eventually block the ENCCs migration and invasion [66]. Further exploring this relationship, Pan et al. [67] discovered that in HSCR patients' diseased intestinal sections, the reduced expression of lncRNA AFAP1-AS1 leads to decreased proliferation, migration, and invasive capacities of enteric neural crest stem cells (ENCSCs). hey also found that lncRNA AFAP1-AS1 can interact with miR-195 through the ceRNA mechanism, specifically regulating the expression of its target gene E2F3, thereby affecting the activity of ENCSCs. This study verified the role of lncRNA AFAP1-AS1 in HSCR at the in *vitro* cellular level, but its potential as a diagnostic or therapeutic target for HSCR still needs validation in *vivo* and clinical samples.

Alterations in lncRNAs expression may also contribute to HSCR by influencing other cell biological functions. For instance, dysregulation of lncRNA FAL1 and lncRNA LOC101926975 leads to cell cycle arrest at the G0/G1 phase [68,69], downregulation of lncRNA LINC00346 promotes cell apoptosis [16], and LncRNA HA117 may possess anti-differentiation functions [70,71]. Other lncRNAs, including MIR143HG, MEG3, LOC100507600, DRAIC, RMST, and ZFAS1 have also been detected to be aberrantly expressed in HSCR [72–77]. However, current research still has limitations, particularly in the lack of the ideal cell model ENCCs, which is the best model for exploring the pathogenesis of HSCR. In the future, we need more methods to elucidate the functions of lncRNAs in HSCR. The specific molecular mechanisms of lncRNA in HSCR are listed in Table 2.

Although some differentially expressed lncRNAs in HSCR have been identified, there are still many yet to be discovered. To this end, Shen et al. [79] utilized microarray technology to analyze lncRNAs in HSCR diseased tissues, and detected 2078 differentially expressed lncRNA—1088 up-regulated and 990 down-regulated (fold change $\geq$2.0, $p < 0.05$). Building on this foundation, Niu et al. [80] revealed key lncRNAs (LINC00619, LINC00924, LINC00261, and DRAIC) and mRNAs

**Table 2**
The expression and function of lncRNAs in HSCR.

| LncRNA | Expression | Function | Mechanism | Ref |
|---|---|---|---|---|
| LINC00346 | ↑ | Inhibits migration and proliferation and promotes apoptosis | Downregulates miR-148a-3p and upregulates DNMT1 | [16] |
| HOTTIP | ↓ | Inhibits proliferation and migration | Downregulates HOXA13 | [64] |
| MIR31HG | ↓ | Inhibits *proliferation and migration* | Regulates miR-31/31*-ITIH5/PIK3CG pathway | [65] |
| AFAP1-AS | ↓ | Suppresses proliferation, migration, and induces the loss of cell stress filament integrity | Upregulates miR-181a and downregulates RAP1B | [66] |
| AFAP1-AS1 | ↓ | Inhibits ENCSC proliferation, differentiation, invasion and migration | Regulates miR-195/E2F3 axis | [67] |
| FAL1 | ↓ | Inhibits migration、proliferation and affects cell cycle | Upregulates miR-637 and downregulates AKT1 | [68] |
| LOC101926975 | ↓ | Suppresses proliferation and induces G0/G1 arrest | Upregulates FGF1 | [69] |
| MEG3 | ↓ | Inhibits migration and proliferation | Regulates miR-770-5p/SRGAP1 pathway | [73] |
| LOC100507600 | ↓ | Inhibits migration and proliferation | Upregulates miR-128-1-3p and downregulates BMI1 | [74] |
| DRAIC | ↑ | Inhibits migration and proliferation | Affects the miR-34a-5p/ITGA6 signal axis | [75] |
| RMST | ↓ | Inhibits migration and proliferation | Regulates SOX2/miR-1251/AHNAK axis | [76] |
| ZFAS1 | ↑ | Inhibits proliferation | Regulates p53、FoxO signal pathways | [77] |
| HN12 | ↑ | Inhibits recipient cell apoptosis | Maintains the function of mitochondria | [78] |

(CYCSs, CCND1, BDKRB, ITGA6, and TNNC1) in the development of HSCR utilizing weighted gene co-expression network analysis. While these genes hold potential as novel clinical biomarkers for HSCR risk assessment, risk score analysis has yet to be employed to appraise the diagnostic relevance of these key lncRNAs and mRNAs in the clinical biomarker context for HSCR. Beyond measuring lncRNA expression in intestinal tissues from HSCR patients, Borrego et al. [81] pioneered the use of enteric precursor cells (EPCs) from both HSCR patients and controls to analyze related lncRNAs. This novel approach led to the discovery of three differentially expressed lncRNAs: SOCS2-AS, MEG3, and NEAT1. In addition, Du et al. [78] found that apoptotic neuronal cells release HN12 via exosomes to mitigate apoptosis in neighboring non-apoptotic cells, thus affecting the process of HSCR. These findings collectively emphasize the profound influence of lncRNAs on the development of the ENS and the onset of HSCR. In contrast, miRNAs have been widely investigated in disease observational studies as a potential diagnostic marker, but there is less research related to lncRNAs. Therefore, future research endeavors should focus on exploring and analyzing the potential utility of this approach as a non-invasive diagnostic molecular biomarker for HSCR diagnosis.

### 2.3. CircRNA

Circular RNAs, a unique class of ncRNAs, are distinguished by their covalently closed loop structure, which confer greater stability compared to linear RNA. Predominantly localized in the cytoplasm, circRNAs primarily act as “molecular sponges” for miRNAs and interact with RNA-binding proteins (RBPs) [82].

Recent studies have highlighted dysregulated circRNA expression in HSCR. Huang et al. [83] utilized microarray technology to analyze diseased intestinal tissues. Subsequent RT-PCR validation confirmed altered expression levels of five specific circRNAs: circRNA-092493, circRNA-101965, circRNA-103118, circRNA-103279, and circRNA-104214, each with AUC values ranging from 0.72 to 0.95, indicating that they have potential implications in HSCR pathogenesis. Another study by Wen et al. [84] revealed that circRNA-CCDC66 was down-regulated in the colon tissue of HSCR patients, and it could inhibit the proliferation and migration of ENCCs via the miR-488-3p/DCX axis. A significant down-regulation of circRNA-ITCH was also found in HSCR patients, which impacts miR-146b-5p, indirectly regulating the expression of RET gene that is crucial in the pathogenesis of HSCR [17]. Chen et al. [85] found that circ-MTCL1 was downregulated in the diseased segments of HSCR, engaging in a molecular sponge effect with miR-145-5p, indirectly modulating SMAD3 expression and suppressing neural cell migration and proliferation. However, circRNAs can also function through other pathways, such as encoding peptides or binding with RBPs, and whether they are also related to affecting the activity of neural cells still needs further study. Additionally, circRNA-PRKCI and circRNA-ZNF609 have been proven to regulate the expression of downstream target genes through the circRNAs-miRNAs-mRNAs network, and participate in the occurrence of HSCR [86,87]. The molecular regulatory mechanisms of circRNAs in HSCR are shown in Table 3.

The unique stability of circRNAs and their tissue-specific expression suggest their potential as biomarkers for HSCR. However, despite some progress in this area, relevant studies on the functions and mechanisms of circRNAs in HSCR are still rare. Future research directions will focus on discovering and validating pathogenic circRNAs through omics sequencing, animal experiments, and multi-center studies, with an aim to explore their potential as therapeutic targets and diagnostic markers. Meanwhile, studying the interactions between circRNAs and other ncRNAs could help us gain insights into the overall landscape of ncRNAs in HSCR.

### 2.4. Proteins or peptides encoded by ncRNAs in HSCR

NcRNAs are typically a class of RNA molecules not known to encode proteins. However, recent studies have found that some ncRNAs in the genome have open reading frames (ORFs), which are capable of translating into biologically active proteins or peptides [88]. NcRNAs, including primary miRNAs (pri-miRNAs), lncRNAs, and circRNAs, are now known to contain small open reading frames (sORFs), which can regulate gene expression during development by encoding proteins or peptides, thereby affecting the occurrence and progression of diseases [89–91].

Studies have revealed that pri-miRNAs can be processed into mature miRNAs that inhibit target gene expression and can also encode a class of proteins or peptides known as miPEPs. For example, 187-aa ORFs have been identified in the primary transcripts of miR-200a, confirming that it can encode miPEP-200a in cancer cells and significantly down-regulate the expression of vimentin, thereby inhibiting the migration of prostate cancer cells [92]. Pei et al. [93] found that lncRNA AFAP1-AS1 can encode a conserved small peptide, ATMLP, which is related to mitochondria function. Its overexpression is notably linked with unfavorable outcomes in non-small cell lung cancer patients. Moreover, more studies have found that circRNAs are similar to mRNAs, can be translated into proteins. For example, circPPP1R12A encoding circPPP1R12A-73aa can activate the Hippo-YAP signaling pathway, thus fostering colon cancer’s proliferation and metastasis [94]. These studies emphasize the role of proteins encoded by ncRNAs in tumor diseases and provide insights into HSCR research.

In HSCR, both miRNA-200a and lncRNA AFAP1-AS1 have been proven to be related to the occurrence of HSCR [29,67]. However, comprehensive research on the function of proteins or peptides encoded by miRNA-200a and lncRNA AFAP1-AS1 in HSCR is still scarce. This gap in knowledge leads to the question: Do proteins or peptides encoded by ncRNAs, such as miPEP-200a and circPPP1R12A-73aa, directly or indirectly influence classic signaling pathways, such as Hippo-YAP, thereby inhibiting the migration and settlement of intestinal neural crest cells in the hindgut and consequently contributing to the development of HSCR? Investigating the involvement of ncRNAs encoded proteins or peptides in the development of HSCR will help further elucidate the pathogenesis of HSCR, and these ncRNAs encoded peptides or proteins may potentially become therapeutic targets and diagnostic markers for HSCR.

### 2.5. ncRNA-mediated epigenetic changes in HSCR

The intricate regulatory interplay of epigenetics is pivotal in elucidating numerous congenital diseases, including HSCR. Within the realm of epigenetic modification, ncRNAs not only directly regulate genes but also interact with DNA methylation, RNA methylation, and histone

**Table 3**
The expression and function of circRNAs in HSCR.

| CircRNA | Expression | Function | Mechanism | Ref |
|---|---|---|---|---|
| Circ-ITCH | ↓ | Inhibits proliferation and migration | Upregulates miR-146-5p and downregulates RET | [17] |
| Circ-CCDC66 | ↓ | Inhibits proliferation and migration | Upregulates miR-488-3p and downregulates DCX | [84] |
| Circ-MTCL1 | ↓ | Inhibits proliferation and migration | Upregulates miR-145-5p and downregulates SMAD3 | [85] |
| Circ-PRKCI | ↓ | Inhibits proliferation and migration | Upregulates miR-1324 and downregulates PLCB1 | [86] |
| Circ-ZNF609 | ↓ | Inhibits proliferation and migration | Upregulates miR-150-5p and downregulates AKT3 | [87] |

modification processes, offering supplemental regulatory avenues for understanding HSCR.

#### 2.5.1. DNA methylation and ncRNAs

DNA methylation predominantly occurs at cytosine bases situated within CpG dinucleotides and often results in gene expression silencing. Integral to this process are the maintenance methyltransferases: DNMT1, DNMT3A, and DNMT3B. Extensive research underscores the pivotal roles these methyltransferases assume in both intestinal and ENCCs development [95–97]. Villalba-Benito et al. [98] observed a reduction in the overall level of DNA methylation in EPCs derived from HSCR patients. Furthermore, aberrant DNA methylation patterns were found in certain key genes associated with ENS development, such as RET, GFRA4, EDNRB, SOX10, PHOX2B, and NRG1 [99–102]. Intriguingly, Villalba-Benito et al. [98] discerned that specific ncRNAs related to HSCR, such as MEG3, AFAP1-AS, IPW, NR2F1-AS1, and miR-195, exhibited aberrant DNA methylation patterns in differential methylation region (DMR) analysis. Notably, the aberrant expression of MEG3, AFAP1-AS and miR-195 has been shown to inhibit the migration and proliferation of ENCCs [38,66,73]. In another study, Tang et al. [37] found that the downregulation of miR-141 in colon tissues of HSCR patients was attributed to the hypermethylation of CpG islands in the promoter region of the gene, further highlighting the significant influence of DNA methylation on ncRNA regulation. Additionally, ncRNAs can target DNMTs for regulation. Li et al. [16] discovered that LINC00346 can serve as an ceRNA, regulating the expression of DNMT1 at the post-transcriptional level and reducing DNMT1 protein synthesis; DNMT1 is closely related to the occurrence of HSCR.

In summary, there is a complex regulatory network between ncRNA and DNMTs. The methylation status of ncRNA gene promoter is regulated by DNMTs, and ncRNAs can also regulate the expression of DNMTs. This intricate interaction may be a key part of the pathogenesis of HSCR.

#### 2.5.2. m6A methylation and ncRNAs

N6-methyladenosine (m6A) methylation stands as a predominant internal modification in eukaryotic mRNA. Functionally, this methylation governs aspects such as mRNA splicing, translation, and stability, while also influencing miRNA processing and maturation. This molecular modification is catalyzed by METTL3, METTL14 and WTAP, whereas m6A removal is performed by the demethylases FTO and ALKBH5. The recognition of m6A involves RNA-binding proteins, such as YTHDF1, YTHDF2, and YTHDF3 [103]. Delving into transcriptomic insights, it's discerned that the absence of METTL3 or METTL14 impacts the expression of transcripts pivotal for neurogenesis, the cell cycle, and neuronal development [104]. Huang et al. [105] found that the expression of METTL3 was downregulated in HSCR and could inhibit the migration and proliferation of ENCCs by regulating the translation level of YAP. Recent findings underscore the decline of overall m6A levels in HSCR lesion tissues, highlighting a crucial link between m6A and HSCR [106]. In addition, m6A modification can also mediate pri-miRNAs processing and promote miRNAs maturation. Zhang et al. [107] found that METTL3 could accelerate the maturation of miR-150 by regulating the m6A methylation of pri-miR-150, exacerbating the progression of neuropathic pain. Conversely, miRNAs can also be involved in disease by regulating m6A methylation-related genes. Wei et al. [108] showed that in non-small cell lung cancer, miR-600 could affect the migration invasion of tumor cells by regulating the expression of METTL3. These series of studies emphasize the mutual regulatory relationship between ncRNAs and m6A. However, m6A is still understudied in HSCR. We need to further explore whether the decreased m6A methylation levels in HSCR lesion segments are related to ncRNAs, and whether the variation of m6A affects the generation of related ncRNAs.

#### 2.5.3. Histone modification and ncRNAs

Histones, which are the fundamental chromatin protein components, interact with DNA to shape the nucleosome structure. Nucleosomesare are composed of eight histone molecules: H2A, H2B, H3, and H4, collectively forming the nucleosome's octameric structure [109]. It's pivotal to understand the role that modifications of these histones, including methylation, acetylation, deacetylation, and phosphorylation, play in steering the transcriptional activity of DNA [110]. The dynamics of histone modifications can either promote or restrain the transcription of specific gene regions [9]. Recent studies have shown that histone methylation and acetylation are intricately tied to the development of NCCs. Zhu et al. [111] demonstrated how the HOXB5 protein complex can alter the methylation status of the RET gene, thus impacting its expression. Notably, any deviation in RET expression could pave the way for HSCR.

In related studies, a reduction in the expression of the histone regulatory factor MeCP2, which is associated with HSCR, has been observed. Zhou et al. [112] documented that curbing the expression of MeCP2 stunted the proliferative capacity of cells. Drawing from this, it was hypothesized that miR-34b could influence its expression by latching onto the 3′-UTR of MeCP2. However, a consistency was observed as miR-34b expression remained largely unchanged between the case and control groups. Furthermore, the enzyme histone methyltransferase, known as Zeste homolog 2 (EZH2), has been proven to mute the expression of PAX3, ZIC1, and SOX10 related to ENCCs development through H3K27 trimethylation modification [113]. In other diseases, EZH2 has been observed to regulate H3K27 trimethylation of miRNA [114], while miRNA can in turn modulate the expression of EZH2 [115]. This interplay underscores the intricate dance between ncRNA and histone modifications. Exploring this reciprocal regulatory mechanism not only enriches our comprehension of HSCR's pathogenesis but also uncovers promising avenues for novel diagnostic and therapeutic modalities centered on ncRNA orchestration.

## 3. High-throughput sequencing technologies and ncRNAs

With the advent of high-throughput sequencing technology and bioinformatics, the study of ncRNAs has undergone a transformation. Utilizing both microarrays and next-generation sequencing, researchers have identified numerous differentially expressed miRNAs, lncRNAs, and circRNAs in HSCR tissues, thereby laying the foundation for comprehensive mechanistic and functional explorations [27,81,83]. RNA sequencing, illustrating these technological advances, enables a more rigorous analysis of the transcriptome. This approach enriches our understanding of the transcriptomic landscape and reveals differentially expressed ncRNAs specific to HSCR tissues. Simultaneously, the deployment of bioinformatics tools for dissecting differential gene expression, pathway enrichment, and mapping out miRNAs-mRNAs, lncRNAs-miRNAs, and circRNAs-miRNAs interaction networks provides a clearer picture of pivotal ncRNAs and the precise pathways they influence [116,117]. The specific molecular mechanism is illustrated in Fig. 3.

Furthermore, the innovative single-cell RNA sequencing (scRNA-Seq) not only demystifies the cellular diversity of HSCR and its associated complications [118,119], but also offers unparalleled insights into varying ncRNAs expression patterns across distinct cell types within the affected tissues. This detailed analysis will enhance our understanding of ncRNAs' role in HSCR and shed light on its pathogenesis.

## 4. Discussion

This review comprehensively introduces the differential expression patterns of ncRNAs in HSCR and their biological significance. We reviewed the recent regulatory roles of miRNAs, lncRNAs, and circRNAs in the development of the Enteric Nervous System (ENS) and the pathogenesis of HSCR, highlighting their interactions with epigenetic mechanisms such as DNA methylation, RNA methylation, and histone modifications. Given the diversity and complexity of ncRNAs'

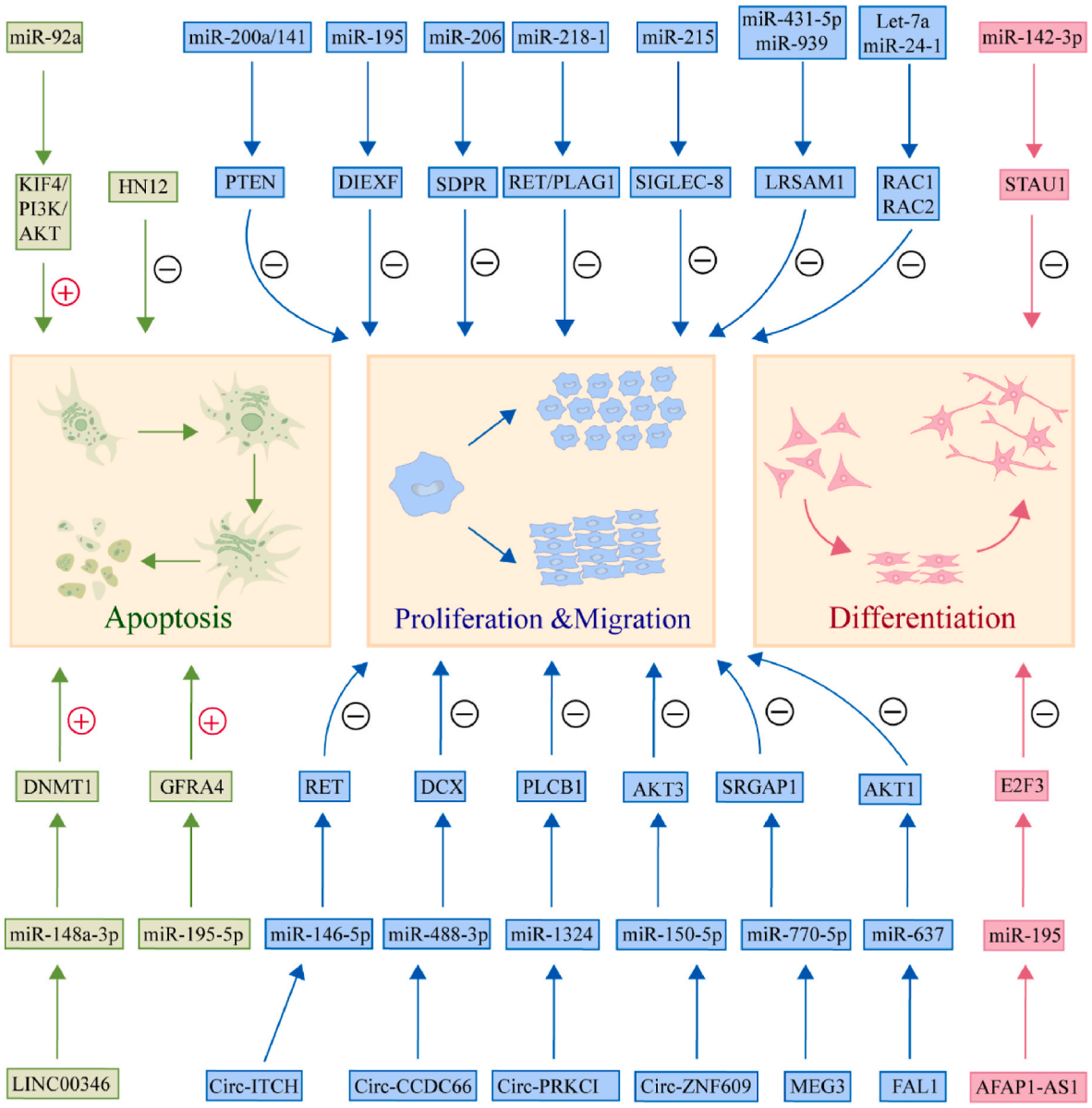


**Fig. 3.** NcRNAs related to cell apoptosis, proliferation, migration, and differentiation in HSCR. Green represents ncRNAs involved in influencing cell apoptosis, blue indicates ncRNAs involved in cell migration and proliferation, and red symbolizes ncRNAs involved in cell differentiation. Moreover, arrows and symbols are used to the regulatory direction of various ncRNAs on their target genes or pathways (where "+" signifies promotion and "-" indicates inhibition).

regulatory mechanisms, our current understanding of their functions in HSCR is incomplete. To address this gap, it's essential to devise ncRNAs-based intervention strategies that delve into ncRNAs' interactions with target genes and related pathways in HSCR. Currently, research on ncRNAs in HSCR is primarily limited to the molecular and cellular level, with a lack of validation in animal models. Therefore, using intestinal neural crest cells and animals as experimental models is crucial. Moreover, the distinct expression patterns of ncRNAs in HSCR tissues reveal their potential as diagnostic and prognostic biomarkers. Some studies suggest that analyzing the expression levels of ncRNAs from tissues, plasma, or exosomes can effectively diagnose or assess the risk of HSCR. However, the challenge remains that there is currently a lack of multi-center, large-scale clinical samples to validate the reliability and accuracy of ncRNAs as molecular diagnostic markers. This is also an important direction in the clinical translation of ncRNAs research. In recent years, studies have also found that ncRNAs can encode biologically active proteins or peptides, which are closely related to the occurrence of some diseases. However, research related to proteins and peptides encoded by ncRNAs in HSCR is still in its infancy, mainly focusing on the regulatory effects of ncRNAs towards mRNAs. Looking forward, we should explore whether the proteins or peptides encoded by ncRNAs are related to the occurrence of HSCR. At the same time, by utilizing advanced technologies, such as spatial transcriptomics or scRNA-Seq, we can gain a deeper understanding of the roles of ncRNAs in HSCR, revealing the molecular complexity of ncRNAs regulation. This approach will help us establish a more comprehensive model to explain the importance of ncRNAs in the pathogenesis of HSCR.

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## CRediT authorship contribution statement

Yang Yang: Writing - original draft. Xinwei Hou: literature search.

Chen Wang, Qinming Chen, Yi Lu, Daiyue Yu: reviewed the manuscript. Kai Wu: guide the project and revise the manuscript. All authors contributed to the article and approved the submitted version.

## Abbreviations

| | |
|---|---|
| HSCR | Hirschsprung's disease |
| ENS | nteric nervous system |
| ncRNA | non-coding RNA |
| nt | nucleotide |
| miRNA | microRNA |
| lncRNA | long non-coding RNA |
| RBPs | RNA-binding proteins |
| ENCSCs | enteric neural crest stem cells |
| circRNA | circular RNA |
| piRNA | piwi-interacting RNA |
| ceRNA | competing endogenous RNA |
| 3′-UTR | 3′-untranslated region |
| ORFs | open reading frames |
| sORFs | small open reading frames |
| pri-miRNAs | primary miRNAs |
| ENCC | enteric neural crest cells |
| NCC | neural crest cell |
| m6A | N6-methyladenosine |
| EPC | enteric precursor cell |
| EZH2 | Zeste homolog 2 |
| AUC | area under the curve |
| ROC | receiver operating characteristic |
| scRNA-Seq | single-cell RNA sequencing |

## References


[1] J. Amiel, S. Lyonnet, Hirschsprung disease, associated syndromes, and genetics: a review, J. Med. Genet. 38 (11) (2001) 729–739, https://doi.org/10.1136/jmg.38.11.729.

[2] S. Li, Y. Zhang, K. Li, Y. Liu, S. Chi, Y. Wang, et al., Update on the pathogenesis of the hirschsprung-associated enterocolitis, Int. J. Mol. Sci. 24 (5) (2023), https://doi.org/10.3390/ijms24054602.

[3] W. Huo, P. Cai, M. Chen, H. Li, J. Tang, C. Xu, et al., The relationship between prenatal exposure to bp-3 and hirschsprung's disease, Chemosphere 144 (2016) 1091–1097, https://doi.org/10.1016/j.chemosphere.2015.09.019.

[4] J.M. Tilghman, A.Y. Ling, T.N. Turner, M.X. Sosa, N. Krumm, S. Chatterjee, et al., Molecular genetic anatomy and risk profile of hirschsprung's disease, N. Engl. J. Med. 380 (15) (2019) 1421–1432, https://doi.org/10.1056/NEJMoa1706594.

[5] A. Sanchez-Mejias, R.M. Fernandez, M. Lopez-Alonso, G. Antinolo, S. Borrego, New roles of ednrb and edn3 in the pathogenesis of hirschsprung disease, Genet. Med. 12 (1) (2010) 39–43, https://doi.org/10.1097/GIM.0b013e3181c371b0.

[6] A. Torroglosa, M.M. Alves, R.M. Fernandez, G. Antinolo, R.M. Hofstra, S. Borrego, Epigenetics in ens development and hirschsprung disease, Dev. Biol. 417 (2) (2016) 209–216, https://doi.org/10.1016/j.ydbio.2016.06.017.

[7] M. Ruiz-Ferrer, A. Torroglosa, B. Luzon-Toro, R.M. Fernandez, G. Antinolo, L. M. Mulligan, et al., Novel mutations at ret ligand genes preventing receptor activation are associated to hirschsprung's disease, J. Mol. Med. 89 (5) (2011) 471–480, https://doi.org/10.1007/s00109-010-0714-2.

[8] R. Diposarosa, N.A. Bustam, E. Sahiratmadja, P.S. Susanto, Y. Sribudiani, Literature review: enteric nervous system development, genetic and epigenetic regulation in the etiology of hirschsprung's disease, Heliyon 7 (6) (2021) e7308, https://doi.org/10.1016/j.heliyon.2021.e.07308.

[9] A. Torroglosa, L. Villalba-Benito, B. Luzon-Toro, R.M. Fernandez, G. Antinolo, S. Borrego, Epigenetic mechanisms in hirschsprung disease, Int. J. Mol. Sci. 20 (13) (2019), https://doi.org/10.3390/ijms20133123.

[10] F.J. Slack, A.M. Chinnaiyan, The role of non-coding rnas in oncology, Cell 179 (5) (2019) 1033–1055, https://doi.org/10.1016/j.cell.2019.10.017.

[11] Z.T. Yao, Y.M. Yang, M.M. Sun, Y. He, L. Liao, K.S. Chen, et al., New insights into the interplay between long non-coding rnas and rna-binding proteins in cancer, Cancer Commun. 42 (2) (2022) 117–140, https://doi.org/10.1002/cac2.12254.

[12] Y.Y. Wu, H.C. Kuo, Functional roles and networks of non-coding rnas in the pathogenesis of neurodegenerative diseases, J. Biomed. Sci. 27 (1) (2020) 49, https://doi.org/10.1186/s1292902000636-z.

[13] E.J. Sohn, H.T. Park, Microrna mediated regulation of schwann cell migration and proliferation in peripheral nerve injury, BioMed Res. Int. 2018 (2018) 8198365, https://doi.org/10.1155/2018/8198365.

[14] O. Rezaei, T.K. Honarmand, M. Hajiesmaeili, M. Taheri, S. Ghafouri-Fard, Non-coding rnas participate in the pathogenesis of neuroblastoma, Front. Oncol. 11 (2021) 617362, https://doi.org/10.3389/fonc.2021.617362.

[15] Y. Daiyue, Y. Yang, H. Zhaorong, L. Yi, W. Chen, L. Caiyun, et al., Plasma exosomal mir-199a-3p downregulates cell proliferation and migration in hirschsprung's disease by targeting mtor, Pediatr. Surg. Int. 39 (1) (2022) 54, https://doi.org/10.1007/s00383-022-05337-2.

[16] L. Li, X. Li, X. Wang, W. Liu, R. Wu, Aberrant expression of linc00346 regulates cell migration and proliferation via competitively binding to mirna-148a-3p/dnmt1 in hirschsprung's disease, Pediatr. Surg. Int. 38 (9) (2022) 1273–1281, https://doi.org/10.1007/s.00383-022-05144-9.

[17] R.P. Xia, F. Zhao, T.D. Ma, C.J. Zou, G. Xu, C.G. Zhou, Circ-itch overexpression promoted cell proliferation and migration in hirschsprung disease through mir-146b-5p/ret axis, Pediatr. Res. 92 (4) (2022) 1008–1016, https://doi.org/10.1038/s41390-021-01860-5.

[18] F.J. Slack, A.M. Chinnaiyan, The role of non-coding rnas in oncology, Cell 179 (5) (2019) 1033–1055, https://doi.org/10.1016/j.cell.2019.10.017.

[19] M. Esteller, Non-coding rnas in human disease, Nat. Rev. Genet. 12 (12) (2011) 861–874, https://doi.org/10.1038/nrg3074.

[20] X. Huang, X. Zhou, Q. Hu, B. Sun, M. Deng, X. Qi, et al., Advances in esophageal cancer: a new perspective on pathogenesis associated with long non-coding rnas, Cancer Lett. 413 (2018) 94–101, https://doi.org/10.1016/j.canlet.2017.10.046.

[21] C.X. Liu, L.L. Chen, Circular rnas: characterization, cellular roles, and applications, Cell 185 (12) (2022) 2016–2034, https://doi.org/10.1016/j.cell.2022.04.021.

[22] T.R. Cech, J.A. Steitz, The noncoding rna revolution-trashing old rules to forge new ones, Cell 157 (1) (2014) 77–94, https://doi.org/10.1016/j.cell.2014.03.008.

[23] H.O. Iwakawa, Y. Tomari, The functions of micrornas: mrna decay and translational repression, Trends Cell Biol. 25 (11) (2015) 651–665, https://doi.org/10.1016/j.tcb.2015.07.0.11.

[24] L.S. Kristensen, T. Jakobsen, H. Hager, J. Kjems, The emerging roles of circrnas in cancer and oncology, Nat. Rev. Clin. Oncol. 19 (3) (2022) 188–206, https://doi.org/10.1038/s41571-021-00585-y.

[25] M.R. Fabian, N. Sonenberg, W. Filipowicz, Regulation of mrna translation and stability by micrornas, Annu. Rev. Biochem. 79 (2010) 351–379, https://doi.org/10.1146/annurev-biochem-060308-103103.

[26] Y. Peng, C.M. Croce, The role of micrornas in human cancer, Signal Transduct. Targeted Ther. 1 (2016) 15004, https://doi.org/10.1038/sigtrans.2015.4.

[27] S. Li, S. Wang, Z. Guo, H. Wu, X. Jin, Y. Wang, et al., Mirna profiling reveals dysregulation of ret and ret-regulating pathways in hirschsprung's disease, PLoS One 11 (3) (2016) e150222, https://doi.org/10.1371/journal.pone.0150222.

[28] Z.G. Gao, Q.J. Chen, M. Shao, Y.Z. Qian, L.F. Zhang, Y.B. Zhang, et al., Preliminary identification of key mirnas, signaling pathways, and genes associated with hirschsprung's disease by analysis of tissue microrna expression profiles, World Journal of Pediatrics 13 (5) (2017) 489–495, https://doi.org/10.1007/s12519-017-0064-z.

[29] H. Li, J. Tang, H. Lei, P. Cai, H. Zhu, B. Li, et al., Decreased mir-200a/141 suppress cell migration and proliferation by targeting pten in hirschsprung's disease, Cell. Physiol. Biochem. 34 (2) (2014) 543–553, https://doi.org/10.1159/000363021.

[30] C.Y. Ji, M.X. Yuan, L.J. Chen, H.Q. Gao, T. Zhang, Q. Yin, Mir-92a represses the viability and migration of nerve cells in hirschsprung's disease by regulating the klf4/pi3k/akt pathway, Acta Neurobiol. Exp. 82 (3) (2022) 336–346, https://doi.org/10.55782/ane-2022-032.

[31] G. Wang, H. Wang, L. Zhang, F. Guo, X. Wu, Y. Liu, Mir-195-5p inhibits proliferation and invasion of nerve cells in hirschsprung disease by targeting gfra4, Mol. Cell. Biochem. 476 (5) (2021) 2061–2073, https://doi.org/10.1007/s11010-021-04055-y.

[32] G. Wang, F. Guo, H. Wang, W. Liu, L. Zhang, M. Cui, et al., Downregulation of microrna-483-5p promotes cell proliferation and invasion by targeting gfra4 in hirschsprung's disease, DNA Cell Biol. 36 (11) (2017) 930–937, https://doi.org/10.1089/dna.2017.3821.

[33] J. Mi, D. Chen, M. Wu, W. Wang, H. Gao, Study of the effect of mir-124 and the sox9 target gene in hirschsprung's disease, Mol. Med. Rep. 9 (5) (2014) 1839–1843, https://doi.org/10.3892/mmr.2014.2022.

[34] S. Yang, F. Dong, D. Li, H. Sun, B. Wu, T. Sun, et al., Persistent distention of colon damages interstitial cells of cajal through ca(2+) -erk-ap-1-mir-34c-scf deregulation, J. Cell Mol. Med. 21 (9) (2017) 1881–1892, https://doi.org/10.1111/jcmm.13108.

[35] Z. Xu, Y. Yan, B. Gu, W. Cai, Y. Wang, Up-regulation of microrna-424 causes an imbalance in akt phosphorylation and impairs enteric neural crest cell migration in hirschsprung disease, Int. J. Mol. Sci. 24 (7) (2023), https://doi.org/10.3390/ijms24076700.

[36] N. Budi Gunadi, A.S. Kalim, W. Santiko, F.D. Musthofa, K. Iskandar, et al., Aberrant expressions of mirna-206 target, fn1, in multifactorial hirschsprung disease, Orphanet J. Rare Dis. 14 (1) (2019) 5, https://doi.org/10.1186/s13023-018-0973-5.

[37] W. Tang, J. Qin, J. Tang, H. Zhang, Z. Zhou, B. Li, et al., Aberrant reduction of mir-141 increased cd47/cul3 in hirschsprung's disease, Cell. Physiol. Biochem. 32 (6) (2013) 1655–1667, https://doi.org/10.1159/000356601.

[38] H. Lei, J. Tang, H. Li, H. Zhang, C. Lu, H. Chen, et al., Mir-195 affects cell migration and cell proliferation by down-regulating diexf in hirschsprung's disease, BMC Gastroenterol. 14 (2014) 123, https://doi.org/10.1186/1471-230X-14-123.

[39] W. Tang, J. Tang, J. He, Z. Zhou, Y. Qin, J. Qin, et al., Slit2/robo1-mir-218-1-ret/plag1: a new disease pathway involved in hirschsprung's disease, J. Cell Mol. Med. 19 (6) (2015) 1197–1207, https://doi.org/10.1111/jcmm.12454.

[40] A. Sharan, H. Zhu, H. Xie, H. Li, J. Tang, W. Tang, et al., Down-regulation of mir-206 is associated with hirschsprung disease and suppresses cell migration and proliferation in cell models, Sci. Rep. 5 (2015) 9302, https://doi.org/10.1038/srep09302.
[41] D. Zhu, H. Xie, H. Li, P. Cai, H. Zhu, C. Xu, et al., Nidogen-1 is a common target of micrornas mir-192/215 in the pathogenesis of hirschsprung's disease, J. Neurochem. 134 (1) (2015) 39–46, https://doi.org/10.1111/jnc.13118.
[42] H. Lei, H. Li, H. Xie, C. Du, Y. Xia, W. Tang, Role of mir-215 in hirschsprung's disease pathogenesis by targeting siglec-8, Cell. Physiol. Biochem. 40 (6) (2016) 1646–1655, https://doi.org/10.1159/000453214.
[43] G. Chen, C. Du, Z. Shen, L. Peng, H. Xie, R. Zang, et al., Microrna-939 inhibits cell proliferation via targeting lrsam1 in hirschsprung's disease, Aging (Albany NY) 9 (12) (2017) 2471–2479, https://doi.org/10.18632/aging.101331.
[44] W. Pan, H. Yu, B. Zheng, Y. Gao, P. Li, Q. Huang, et al., Upregulation of mir-369-3p suppresses cell migration and proliferation by targeting sox4 in hirschsprung's disease, J. Pediatr. Surg. 52 (8) (2017) 1363–1370, https://doi.org/10.1016/j.jpedsurg.2017.04.002.
[45] Z. Zhi, H. Zhu, X. Lv, C. Lu, Y. Li, F. Wu, et al., Igf2-derived mir-483-3p associated with hirschsprung's disease by targeting fhl1, J. Cell Mol. Med. 22 (10) (2018) 4913–4921, https://doi.org/10.1111/jcmm.13756.
[46] B. Hu, L. Cao, X.Y. Wang, L. Li, Downregulation of microrna-431-5p promotes enteric neural crest cell proliferation via targeting lrsam1 in hirschsprung's disease, Dev. Growth Differ. 61 (4) (2019) 294–302, https://doi.org/10.1111/dgd.12606.
[47] L. Wu, W. Yuan, J. Chen, Z. Zhou, Y. Shu, J. Ji, et al., Increased mir-214 expression suppresses cell migration and proliferation in hirschsprung disease by interacting with plagl2, Pediatr. Res. 86 (4) (2019) 460–470, https://doi.org/10.1038/s41390-019-0324-9.
[48] Y. Wang, Q. Jiang, A. Chakravarti, H. Cai, Z. Xu, W. Wu, et al., Microrna-4516-mediated regulation of mapk10 relies on 3' utr cis-acting variants and contributes to the altered risk of hirschsprung disease, J. Med. Genet. 57 (9) (2020) 634–642, https://doi.org/10.1136/jmedgenet-2019-106615.
[49] G. Du, X. Wang, Y. Wu, Y. Zhang, W. Liu, R. Wu, Downregulation of mir-140-5p affects the pathogenesis of hscr by targeting egr2, Pediatr. Surg. Int. 36 (8) (2020) 883–890, https://doi.org/10.1007/s00383-020-04686-0.
[50] L. Peng, H. Zhang, Y. Su, Q. Shen, C. Du, H. Xie, et al., Lipopolysaccharide enhances adar2 which drives hirschsprung's disease by impairing mir-142-3p biogenesis, J. Cell Mol. Med. 22 (9) (2018) 4045–4055, https://doi.org/10.1111/jcmm.13652.
[51] W. Tang, P. Cai, W. Huo, H. Li, J. Tang, D. Zhu, et al., Suppressive action of mirnas to arp2/3 complex reduces cell migration and proliferation via rac isoforms in hirschsprung disease, J. Cell Mol. Med. 20 (7) (2016) 1266–1275, https://doi.org/10.1111/jcmm.12799.
[52] H. Zheng, D. Wu, H. Chen, J. Bai, Y. Fang, Downregulation of mir-144 blocked the proliferation and invasion of nerve cells in hirschsprung disease by regulating transcription factor ap 4 (tfap4), Pediatr. Surg. Int. 39 (1) (2023) 251, https://doi.org/10.1007/s00383-023-05530-x.
[53] W. Tang, H. Li, J. Tang, W. Wu, J. Qin, H. Lei, et al., Specific serum microrna profile in the molecular diagnosis of hirschsprung's disease, J. Cell Mol. Med. 18 (8) (2014) 1580–1587, https://doi.org/10.1111/jcmm.12348.
[54] M. Hong, X. Li, Y. Li, Y. Zhou, Y. Li, S. Chi, et al., Hirschsprung's disease: key micrornas and target genes, Pediatr. Res. 92 (3) (2022) 737–747, https://doi.org/10.1038/s41390-021-01872-1.
[55] X. Lv, Y. Li, H. Li, L. Zhou, B. Wang, Z. Zhi, et al., Molecular function predictions and diagnostic value analysis of plasma exosomal mirnas in hirschsprung's disease, Epigenomics 12 (5) (2020) 409–422, https://doi.org/10.2217/epi-2019-0190.
[56] J. Zhong, J. Liu, Y. Zheng, X. Xie, Q. He, W. Zhong, et al., Mir-938rs2505901 t>c polymorphism increases hirschsprung disease risk: a case-control study of Chinese children, Pers. Med. 18 (6) (2021) 551–558, https://doi.org/10.2217/pme-2021-0001.
[57] Q. Wu, J. Zhao, Y. Zheng, X. Xie, Q. He, Y. Zhu, et al., Associations between common genetic variants in micrornas and hirschsprung disease susceptibility in southern Chinese children, J. Gene Med. 23 (2) (2021) e3301, https://doi.org/10.1002/jgm.3301.
[58] H. Zhu, P. Cai, D. Zhu, C. Xu, H. Li, J. Tang, et al., A common polymorphism in pre-mir-146a underlies hirschsprung disease risk in han Chinese, Exp. Mol. Pathol. 97 (3) (2014) 511–514, https://doi.org/10.1016/j.yexmp.2014.11.004.
[59] Y. Zheng, T. Lu, X. Xie, Q. He, L. Lu, W. Zhong, Mir-618 rs2682818 c>a polymorphism decreases hirschsprung disease risk in Chinese children, Biosci. Rep. 40 (5) (2020), https://doi.org/10.1042/BSR20193989.
[60] Y. Zheng, Y. Liu, M. Wang, Q. He, X. Xie, L. Lu, et al., Association between mir-492 rs2289030 g>c and susceptibility to hirschsprung disease in southern Chinese children, J. Int. Med. Res. 48 (10) (2020) 1220761232, https://doi.org/10.1177/0300060520961680.
[61] J. Zhang, Z. Zhang, Z. Chen, L. Deng, Integrating multiple heterogeneous networks for novel lncrna-disease association inference, IEEE ACM Trans. Comput. Biol. Bioinf 16 (2) (2019) 396–406, https://doi.org/10.1109/TCBB.2017.2701379.
[62] K. Taniue, N. Akimitsu, The functions and unique features of lncrnas in cancer development and tumorigenesis, Int. J. Mol. Sci. 22 (2) (2021), https://doi.org/10.3390/ijms2.2020632.
[63] Y. Zheng, Z. Zhuo, X. Xie, L. Lu, Q. He, W. Zhong, Negative association between lncrna hottip rs3807598 c>g and hirschsprung disease, Pharmacogn. Pers. Med. 13 (2020) 151–156, https://doi.org/10.2147/PGPM.S249649.
[64] H. Xie, D. Zhu, C. Xu, H. Zhu, P. Chen, H. Li, et al., Long none coding rna hottip/hoxa13 act as synergistic role by decreasing cell migration and proliferation in hirschsprung disease, Biochem. Biophys. Res. Commun. 463 (4) (2015) 569–574, https://doi.org/10.1016/j.bbrc.20.15.05.096.
[65] P. Cai, H. Li, W. Huo, H. Zhu, C. Xu, R. Zang, et al., Aberrant expression of lncrna-mir31hg regulates cell migration and proliferation by affecting mir-31 and mir-31* in hirschsprung's disease, J. Cell. Biochem. 119 (10) (2018) 8195–8203, https://doi.org/10.1002/jcb.26830.
[66] G. Chen, L. Peng, Z. Zhu, C. Du, Z. Shen, R. Zang, et al., Lncrna afap1-as functions as a competing endogenous rna to regulate rap1b expression by sponging mir-181a in the hscr, Int. J. Med. Sci. 14 (10) (2017) 1022–1030, https://doi.org/10.7150/ijms.18392.
[67] W. Pan, A. Wu, H. Yu, Q. Yu, B. Zheng, W. Yang, et al., Involvement of the lncrna afap1-as1/microrna-195/e2f3 axis in proliferation and migration of enteric neural crest stem cells of hirschsprung's disease, Exp. Physiol. 105 (11) (2020) 1939–1949, https://doi.org/10.1113/EP0887.80.
[68] Y. Li, L. Zhou, C. Lu, Q. Shen, Y. Su, Z. Zhi, et al., Long non-coding rna fal1 functions as a cerna to antagonize the effect of mir-637 on the down-regulation of akt1 in hirschsprung's disease, Cell Prolif. 51 (5) (2018) e12489, https://doi.org/10.1111/cpr.12489.
[69] Z. Shen, L. Peng, Z. Zhu, H. Xie, R. Zang, Du C, et al., Downregulated expression of long non-coding rna loc101926975 impairs both cell proliferation and cell cycle and its clinical implication in hirschsprung disease patients, Int. J. Med. Sci. 13 (4) (2016) 292–297, https://doi.org/10.7150/ijms.14187.
[70] H. Liu, Y. Luo, S. Li, S. Wang, N. Wang, X. Jin, Expression profiles of ha117 and its neighboring gene dpf3 in different colon segments of hirschsprung's disease, Int. J. Clin. Exp. Pathol. 7 (7) (2014) 3966–3974.
[71] Y. Luo, S. Li, Y. Teng, N. Wang, L. Li, H. Liu, et al., Differential expression of foxa1, dusp6, and ha117 in colon segments of hirschsprung's disease, Int. J. Clin. Exp. Pathol. 8 (4) (2015) 3979–3986.
[72] C. Du, Z. Shen, R. Zang, H. Xie, H. Li, P. Chen, et al., Negative feedback circuitry between mir143hg and rbm24 in hirschsprung disease, Biochim. Biophys. Acta 1862 (11) (2016) 2127–2136, https://doi.org/10.1016/j.bbadis.2016.08.017.
[73] H. Li, B. Li, D. Zhu, H. Xie, C. Du, Y. Xia, et al., Downregulation of lncrna meg3 and mir-770-5p inhibit cell migration and proliferation in hirschsprung's disease, Oncotarget 8 (41) (2017) 69722–69730, https://doi.org/10.18632/oncotarget.19207.
[74] Y. Su, Z. Wen, Q. Shen, H. Zhang, L. Peng, G. Chen, et al., Long non-coding rna loc100507600 functions as a competitive endogenous rna to regulate bmi1 expression by sponging mir128-1-3p in hirschsprung's disease, Cell Cycle 17 (4) (2018) 459–467, https://doi.org/10.1080/15384101.2017.1403688.
[75] C. Sun, B. Xu, L. Wang, Y. Su, Lncrna draic regulates cell proliferation and migration by affecting the mir-34a-5p/itga6 signal axis in hirschsprung's disease, Ups. J. Med. Sci. 126 (2021), https://doi.org/10.48101/ujms.v126.7895.
[76] L. Zhou, Z. Zhi, P. Chen, C. Du, B. Wang, X. Fang, et al., Lncrna-rmst functions as a transcriptional co-regulator of sox2 to regulate mir-1251 in the progression of hirschsprung's disease, Front. Pediatr. 10 (2022) 749107, https://doi.org/10.3389/fped.2022.749107.
[77] Y. Wang, P. Cai, J. Wang, Clinical significance and biological effect of zfas1 in hirschsprung's disease and preliminary exploration of its underlying mechanisms using integrated bioinformatics analysis, Ir. J. Med. Sci. 191 (6) (2022) 2669–2675, https://doi.org/10.1007/s11845-021-02906-7.
[78] C. Du, H. Xie, R. Zang, Z. Shen, H. Li, P. Chen, et al., Apoptotic neuron-secreted hn12 inhibits cell apoptosis in hirschsprung's disease, Int. J. Nanomed. 11 (2016) 5871–5881, https://doi.org/10.2147/IJN.S114838.
[79] Z. Shen, C. Du, R. Zang, H. Xie, W. Lv, H. Li, et al., Microarray expression profiling of dysregulated long non-coding rnas in hirschsprung's disease reveals their potential role in molecular diagnosis, Neurogastroenterol, Motil 28 (2) (2016) 266–273, https://doi.org/10.1111/nmo.12722.
[80] X. Niu, Y. Xu, N. Gao, A. Li, Weighted gene coexpression network analysis reveals the critical lncrnas and mrnas in development of hirschsprung's disease, J. Comput. Biol. 27 (7) (2020) 1115–1129, https://doi.org/10.1089/cmb.2019.0261.
[81] A. Torroglosa, L. Villalba-Benito, R.M. Fernandez, B. Luzon-Toro, M.J. Moya-Jimenez, G. Antinolo, et al., Identification of new potential lncrna biomarkers in hirschsprung disease, Int. J. Mol. Sci. 21 (15) (2020), https://doi.org/10.3390/ijms21155534.
[82] J. Salzman, Circular rna expression: its potential regulation and function, Trends Genet. 32 (5) (2016) 309–316, https://doi.org/10.1016/j.tig.2016.03.002.
[83] S.G. Huang, Y. Cheng, D. Li, C. Sun, F. Fang, W.L. Guo, Systematic screen of potential circular rna biomarkers of hirschsprung's disease, Transl. Pediatr. 11 (1) (2022) 10–19, https://doi.org/10.21037/tp-21-392.
[84] Z. Wen, Q. Shen, H. Zhang, Y. Su, Z. Zhu, G. Chen, et al., Circular rna ccdc66 targets dcx to regulate cell proliferation and migration by sponging mir-488-3p in hirschsprung's disease, J. Cell. Physiol. 234 (7) (2019) 10576–10587, https://doi.org/10.1002/jcp.27733.
[85] W. Chen, L. Caiyun, Y. Yang, H. Xinwei, L. Nan, Y. Jiaming, et al., Circular rna mtcl1 targets smad3 by sponging mir-145-5p for regulation of cell proliferation and migration in hirschsprung's disease, Pediatr. Surg. Int. 40 (1) (2023) 25, https://doi.org/10.1007/s00383-023-05621-9.
[86] L. Zhou, Y. Li, W. Jiang, H. Zhang, Z. Wen, Y. Su, et al., Down-regulation of circ-prkci inhibits cell migration and proliferation in hirschsprung disease by suppressing the expression of mir-1324 target plcb1, Cell Cycle 17 (9) (2018) 1092–1101, https://doi.org/10.1080/15384101.2018.1480210.
[87] L. Peng, G. Chen, Z. Zhu, Z. Shen, C. Du, R. Zang, et al., Circular rna znf609 functions as a competitive endogenous rna to regulate akt3 expression by

sponging mir-150-5p in hirschsprung's disease, Oncotarget 8 (1) (2017) 808–818, https://doi.org/10.18632/oncotarget.13656.
[88] D.M. Anderson, C.A. Makarewich, K.M. Anderson, J.M. Shelton, S. Bezprozvannaya, R. Bassel-Duby, et al., Widespread control of calcium signaling by a family of serca-inhibiting micropeptides, Sci. Signal. 9 (457) (2016), https://doi.org/10.1126/scisignal.aaj1460 ra119.
[89] H. Zhou, F. Lou, J. Bai, Y. Sun, W. Cai, L. Sun, et al., A peptide encoded by pri-mirna-31 represses autoimmunity by promoting t(reg) differentiation, EMBO Rep. 23 (5) (2022) e53475, https://doi.org/10.15252/embr.202153475.
[90] J.Z. Huang, M. Chen, D. Chen, X.C. Gao, S. Zhu, H. Huang, et al., A peptide encoded by a putative lncrna hoxb-as3 suppresses colon cancer growth, Mol. Cell 68 (1) (2017) 171–184, https://doi.org/10.1016/j.molcel.2017.09.015.
[91] Z. Song, J. Lin, R. Su, Y. Ji, R. Jia, S. Li, et al., Eif3j inhibits translation of a subset of circular rnas in eukaryotic cells, Nucleic Acids Res. 50 (20) (2022) 11529–11549, https://doi.org/10.1093/nar/gkac980.
[92] M. Kang, B. Tang, J. Li, Z. Zhou, K. Liu, R. Wang, et al., Identification of mipep133 as a novel tumor-suppressor microprotein encoded by mir-34a pri-mirna, Mol. Cancer 19 (1) (2020) 143, https://doi.org/10.1186/s12943-020-01248-9.
[93] H. Pei, Y. Dai, Y. Yu, J. Tang, Z. Cao, Y. Zhang, et al., The tumorigenic effect of lncrna afap1-as1 is mediated by translated peptide atmlp under the control of m (6)a methylation, Adv. Sci. 10 (13) (2023) e2300314, https://doi.org/10.1002/advs.20230.0314.
[94] X. Zheng, L. Chen, Y. Zhou, Q. Wang, Z. Zheng, B. Xu, et al., A novel protein encoded by a circular rna circppp1r12a promotes tumor pathogenesis and metastasis of colon cancer via hippo-yap signaling, Mol. Cancer 18 (1) (2019) 47, https://doi.org/10.1186/s12943-019-1010-6.
[95] A. Torroglosa, M.V. Enguix-Riego, R.M. Fernandez, F.J. Roman-Rodriguez, M. J. Moya-Jimenez, J.C. de Agustin, et al., Involvement of dnmt3b in the pathogenesis of hirschsprung disease and its possible role as a regulator of neurogenesis in the human enteric nervous system, Genet. Med. 16 (9) (2014) 703–710, https://doi.org/10.1038/gim.2014.17.
[96] L. Villalba-Benito, A. Torroglosa, R.M. Fernandez, M. Ruiz-Ferrer, M.J. Moya-Jimenez, G. Antinolo, et al., Overexpression of dnmt3b target genes during enteric nervous system development contribute to the onset of hirschsprung disease, Sci. Rep. 7 (1) (2017) 6221, https://doi.org/10.1038/s41598-017-06539-8.
[97] J. Ganz, E. Melancon, C. Wilson, A. Amores, P. Batzel, M. Strader, et al., Epigenetic factors dnmt1 and uhrf1 coordinate intestinal development, Dev. Biol. 455 (2) (2019) 473–484, https://doi.org/10.1016/j.ydbio.2019.08.002.
[98] L. Villalba-Benito, D. Lopez-Lopez, A. Torroglosa, C.S. Casimiro-Soriguer, B. Luzon-Toro, R.M. Fernandez, et al., Genome-wide analysis of dna methylation in hirschsprung enteric precursor cells: unraveling the epigenetic landscape of enteric nervous system development, Clin. Epigenet. 13 (1) (2021) 51, https://doi.org/10.1186/s13148-021-01040-6.
[99] W. Tang, B. Li, X. Xu, Z. Zhou, W. Wu, J. Tang, et al., Aberrant high expression of nrg1 gene in hirschsprung disease, J. Pediatr. Surg. 47 (9) (2012) 1694–1698, https://doi.org/10.1016/j.jpedsurg.2012.03.061.
[100] G. Wang, L. Zhang, H. Wang, M. Cui, W. Liu, Y. Liu, et al., Demethylation of gfra4 promotes cell proliferation and invasion in hirschsprung disease, DNA Cell Biol. 37 (4) (2018) 316–324, https://doi.org/10.1089/dna.2017.3928.
[101] Y.R. Liu, F. Ba, L.J. Cheng, X. Li, S.W. Zhang, S.C. Zhang, Efficacy of sox10 promoter methylation in the diagnosis of intestinal neuronal dysplasia from the peripheral blood, Clin. Transl. Gastroenterol. 10 (12) (2019) e93, https://doi.org/10.14309/ctg.0000000000000093.
[102] W. Tang, B. Li, J. Tang, K. Liu, J. Qin, W. Wu, et al., Methylation analysis of ednrb in human colon tissues of hirschsprung's disease, Pediatr. Surg. Int. 29 (7) (2013) 683–688, https://doi.org/10.1007/s00383-013-3308-6.
[103] X. Jiang, B. Liu, Z. Nie, L. Duan, Q. Xiong, Z. Jin, et al., The role of m6a modification in the biological functions and diseases, Signal Transduct. Targeted Ther. 6 (1) (2021) 74, https://doi.org/10.1038/s41392-020-00450-x.
[104] L. Shu, X. Huang, X. Cheng, X. Li, Emerging roles of n6-methyladenosine modification in neurodevelopment and neurodegeneration, Cells 10 (10) (2021), https://doi.org/10.3390/cells10102694.
[105] Z. Huang, C. Luo, X. Hou, D. Yu, Y. Su, X. Li, et al., The m(6)a methyltransferase mettl3 affects cell proliferation and migration by regulating yap expression in hirschsprung disease, Pediatr. Surg. Int. 39 (1) (2023) 126, https://doi.org/10.1007/s00383-023-05421-1.
[106] B. Wang, X. Fang, X. Sun, C. Du, L. Zhou, X. Lv, et al., M(6)a demethylase alkbh5 suppresses proliferation and migration of enteric neural crest cells by regulating tagln in hirschsprung's disease, Life Sci. 278 (2021) 119577, https://doi.org/10.1016/j.lfs.2021.119577.
[107] L. Zhang, X. Zhao, J. Wang, Y. Jin, M. Gong, Y. Ye, et al., Mettl3 suppresses neuropathic pain via modulating n6-methyladenosine-dependent primary mir-150 processing, Cell Death Dis. 8 (1) (2022) 80, https://doi.org/10.1038/s41420-022-00880-2.
[108] W. Wei, B. Huo, X. Shi, Mir-600 inhibits lung cancer via downregulating the expression of mettl3, Cancer Manag. Res. 11 (2019) 1177–1187, https://doi.org/10.2147/CMAR.S181058.
[109] P. Tessarz, T. Kouzarides, Histone core modifications regulating nucleosome structure and dynamics, Nat. Rev. Mol. Cell Biol. 15 (11) (2014) 703–708, https://doi.org/10.1038/nrm.3890.
[110] M.E. Neganova, S.G. Klochkov, Y.R. Aleksandrova, G. Aliev, Histone modifications in epigenetic regulation of cancer: perspectives and achieved progress, Semin. Cancer Biol. 83 (2022) 452–471, https://doi.org/10.1016/j.semcancer.2020.07.015.
[111] J.J. Zhu, M.K. Kam, M.M. Garcia-Barcelo, P.K. Tam, V.C. Lui, Hoxb5 binds to multi-species conserved sequence (mcs+9.7) of ret gene and regulates ret expression, Int. J. Biochem. Cell Biol. 51 (2014) 142–149, https://doi.org/10.1016/j.biocel.2014.04.013.
[112] Z. Zhou, J. Qin, J. Tang, B. Li, Q. Geng, W. Jiang, et al., Down-regulation of mecp2 in hirschsprung's disease, J. Pediatr. Surg. 48 (10) (2013) 2099–2105, https://doi.org/10.1016/j.jpedsurg.2013.07.011.
[113] H. Kim, I.M. Langohr, M. Faisal, M. Mcnulty, C. Thorn, J. Kim, Ablation of ezh2 in neural crest cells leads to aberrant enteric nervous system development in mice, PLoS One 13 (8) (2018) e203391, https://doi.org/10.1371/journal.pone.0203391.
[114] T. Liu, J. Cai, J. Cai, Z. Wang, L. Cai, Ezh2-mirna positive feedback promotes tumor growth in ovarian cancer, Front. Oncol. 10 (2020) 608393, https://doi.org/10.3389/fonc.202.0.608393.
[115] S. Mirzaei, M.H. Gholami, K. Hushmandi, F. Hashemi, A. Zabolian, I. Canadas, et al., The long and short non-coding rnas modulating ezh2 signaling in cancer, J. Hematol. Oncol. 15 (1) (2022) 18, https://doi.org/10.1186/s13045-022-01235-1.
[116] W. Xu, H. Yu, D. Chen, W. Pan, W. Yang, J. Miao, et al., Identifying the potential transcriptional regulatory network in hirschsprung disease by integrated analysis of microarray datasets, World J. Pediatr. Surg. 6 (2) (2023) e547, https://doi.org/10.1136/wjps-2022-000547.
[117] A. Rincon-Riveros, D. Morales, J.A. Rodriguez, V.E. Villegas, L. Lopez-Kleine, Bioinformatic tools for the analysis and prediction of ncrna interactions, Int. J. Mol. Sci. 22 (21) (2021), https://doi.org/10.3390/ijms222111397.
[118] S. He, J. Wang, Y. Huang, F. Kong, R. Yang, Y. Zhan, et al., Intestinal fibrosis in aganglionic segment of hirschsprung's disease revealed by single-cell rna sequencing, Clin. Transl. Med. 13 (2) (2023) e1193, https://doi.org/10.1002/ctm2.1193.
[119] Z. Li, K.N. Lui, S.T. Lau, F.P. Lai, P. Li, P.H. Chung, et al., Transcriptomics of hirschsprung disease patient-derived enteric neural crest cells reveals a role for oxidative phosphorylation, Nat. Commun. 14 (1) (2023) 2157, https://doi.org/10.1038/s41467-023-37928-5.