REVIEW ARTICLE

Non-coding RNAs in Neonatal Necrotizing Enterocolitis

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Abstract

The incomplete understanding of the etiopathogenesis of necrotizing enterocolitis (NEC) contributes to the lack of timely diagnosis and limited therapeutic options. Non-coding RNAs (ncRNAs) have emerged as key regulators of gene expression in various pathways that can modulate various physiological and pathological processes. Despite several studies revealing the role of ncRNAs in intestinal inflammatory diseases in adults, these remain largely unexplored in NEC. In this article, we review the information on ncRNAs that have been specifically identified in NEC or have been noted in other inflammatory bowel disorders that share some of the histopathological abnormalities seen frequently in NEC. We have assimilated the most current research findings on ncRNAs in intestinal diseases. This is an attempt to explore a novel field that has immense potential for future translational and clinical research in preventing, detecting, and treating NEC.

Keywords: Genetic predisposition, Intestinal inflammation, Necrotizing enterocolitis, Neonates, Non-coding RNA, Spontaneous intestinal perforation.

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Impact

- Current information categorizes NEC as a multifactorial, inflammatory bowel necrosis of newborn infants.
- Non-coding RNAs (ncRNAs) may influence the risk of occurrence of NEC.
- ncRNAs may modulate the severity of intestinal injury and consequently the clinical outcome of NEC.
- ncRNAs have been linked with inflammatory intestinal diseases of adults that share histopathological findings with neonatal NEC and, hence, need to be explored.

Introduction

Necrotizing enterocolitis (NEC), an inflammatory necrosis that may involve parts of the small and the large intestine, is one of the most common and serious diseases in premature infants causing significant morbidity and mortality. The etiopathogenesis of NEC in neonates is multifactorial. Prematurity is the prime risk factor for NEC development. In addition, various prenatal and postnatal factors contribute to the disease development and progression such as antenatal steroids, type of feeding, gut dysbiosis, hypoxic-ischemic injury, severe anemia requiring packed red cell transfusion. Clinically, the presenting features include abdominal distension, hematochezia, emesis, and feeding intolerance, which can be associated with subtle changes in vital signs including temperature instability, tachycardia, and lethargy. Abdominal radiography remains the diagnostic tool of choice with pathognomonic sign of *pneumatosis intestinalis*. The disease usually involves ileocolic region and colon; histopathologically, NEC is characterized by exaggerated inflammation, coagulative necrosis, *pneumatosis intestinalis*, intestinal hemorrhage, and reparative changes.[1] The treatment is currently limited to supportive care in an attempt to prevent further injury to the intestine. Despite major advances in neonatology, the options to diagnose and treat NEC are few, and the available strategies have not made a significant impact bringing down the prevalence and improving outcomes. There is a need for more research to explore novel biomarkers and potential therapeutic targets.

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Recently, rapidly growing interest in genetic research along with the availability of in-depth transcriptome sequencing techniques has exponentially expanded our understanding of gene expression and its regulation. This added knowledge has introduced the possibility of a complex interaction between clinical risk factors and genetic susceptibility explaining inter-individual variability of NEC susceptibility, progression, and prognosis. Non-coding RNAs (ncRNAs) have been unraveled recently as one of the key regulators of gene expression. In this review, we aim to provide currently available evidence from human and animal studies on role of ncRNAs in the pathogenesis of NEC. We also present the evidence for ncRNAs in other intestinal diseases that share similar histopathological characteristics with NEC for future direction. We have extensively searched in the databases PubMed, EMBASE, and Scopus after short-listing the keywords to describe the histopathological and clinical features of NEC.

Non-coding RNAs

The ncRNAs, as the name suggests, are RNA molecules that are not translated into proteins. Since first discovered in eukaryotic

cells in 1989, ncRNAs have gained tremendous visibility. About 80–90% of living cell genome is transcribed, however, only less than 2% of that transcribed RNA encodes for protein. Thus, RNAs can be categorized into coding and ncRNAs. ncRNA molecules are further categorized based on function into (1) housekeeping ncRNAs, such as transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs), and (2) regulatory ncRNAs. The ncRNAs can also be categorized into two groups based on their nucleotide size, (1) small ncRNAs (<200 nucleotides), and (2) long ncRNAs (>200 nucleotides). The most studied small ncRNAs are <50 nucleotides long and therefore, to better categorize 50–200 nucleotide-long ncRNAS, a term "mid-size" ncRNAs have been proposed which includes snoRNAs, promoter-associated small RNAs (PASRs), transcription start site-associated RNAs (TSSa-RNAs), and promoter upstream transcripts (PROMPTs).[2,3] Circular RNAs (circ-RNAs) are another variant, which are comprised of a covalently closed continuous loop that lacks the 5′ cap and the 3′ tail.[4] Similarly, pyknons are recognizable non-random sequences that may be repeated mainly in the non-coding genomic DNA.[5] Different types of ncRNAs are depicted in Figure 1. So far, microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), lncRNAs, and circular RNAs (circRNAs) have been studied.

MicroRNAs

MicroRNAs (miRNAs) are endogenous, conserved, 21–23 nucleotide-long ncRNAs involved in posttranscriptional silencing of gene expression.[6] Approximately 1–3% of the mammalian genome is now known to code for miRNAs. MiRNA genes are distributed throughout the genome and can be seen in intronic sequences of protein-coding genes, within intronic or exonic regions of ncRNAs, and even between independent transcription units (intergenic). MiRNAs may carry specific promoters for independent transcription, share promoters with host genes, or could be cotranscribed as a single primary miRNA transcript.[7]

The DNA sequences encoding for mRNAs are first transcribed in the nucleus by the RNA polymerase II-producing primary RNAs (pri-miRNAs). The pri-miRNA is then processed in a stepwise manner by nuclear as well as cytoplasmic endoribonucleases forming mature miRNA. Drosha, a type III ribonuclease located in the nucleus, processes pri-miRNA into ~70 nucleotide-containing precursor (pre-) miRNAs. These oligonucleotides are then translocated into the cytoplasm by the exportin-5 shuttle.[8] In the cytoplasm, this pre-miRNA is further processed by another type III ribonuclease, dicer, into a mature miRNA. The 3′-end of the miRNA binds the Argonaute protein in a specialized oligonucleotide/oligosaccharide-binding fold to form an RNA-induced silencing complex (RISC).[9] RISCs bind approximately complementary sequences in the 3′-untranslated region (UTR)s of target mRNAs and regulate protein output by either promoting mRNA degradation and/or inhibiting translation.[10] Genomic analyses of miRNA-target interactions show conserved complementarity for approximately 6–8 base pairs from position II of the miRNA. This region (nucleotides 2–7 at the 5′ end of the miRNA) is often termed the "seed" sequence for computational miRNA target prediction.[11]

The function of most miRNAs is still unclear. A single miRNA can regulate hundreds of genes, because only a few RNA nucleotides (2 through 7 or 8) are needed to recruit RISC and bind the seed sequence of a target mRNA for repression.[12,13] Many miRNAs are now believed to modulate cellular differentiation, proliferation, apoptosis, inflammation, and stem cell maintenance and may also indicate the timing of various events during development.[6] These features, together with the observation that miRNAs can be secreted and stay stable in plasma, make them prominent, accessible biomarkers as well as therapeutic targets.[14]

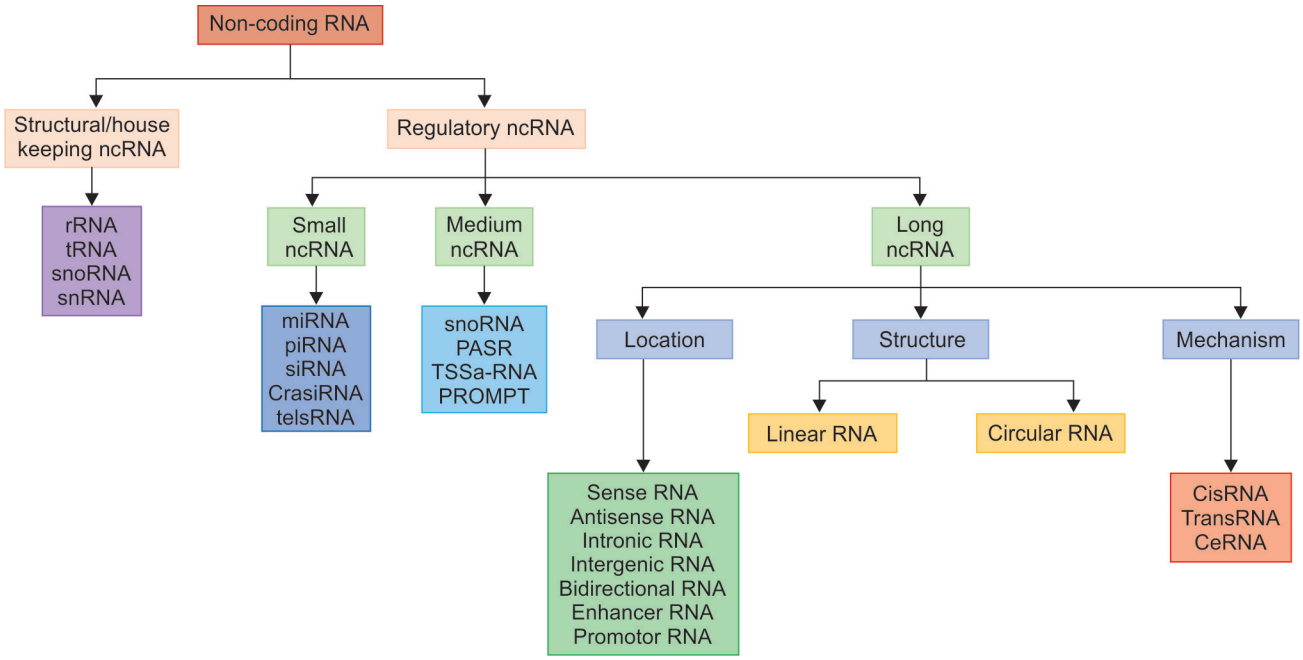


Fig. 1: Classification of non-coding RNAs. ceRNA, competing endogenous RNA; cisRNA, cis-acting RNA; crasiRNA, centromere repeat-associated small interacting RNA; miRNA, microRNA; ncRNA, non-coding RNA; PASR, promoter-associated small RNA; piRNA, piwi-interacting RNA; PROMPT, promoter upstream transcripts; rRNA, ribosomal RNA; siRNA, small interfering RNA; snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; tRNA, transfer RNA; telsRNA, telomere-specific small RNA; transRNA, trans-acting RNA; TSSa-RNA, transcription start site-associated RNAs

Piwi-interacting RNAs

Piwi-interacting RNAs (piRNAs) are 26–31 nucleotide-long ncRNAs that interact with the piwi family of proteins. The transcription process of piRNA is dicer-independent and is activated in the piRNA gene clusters on heterochromatin. Pre-initiation complex (PIC) is formed after recruitment of RNA polymerase II, and other transcription factors that in turn initiate piRNA transcription and eventually produce pre-piRNA. Once formed, pre-piRNA is translocated into the cytoplasm. In the cytoplasm, 5′-end of pre-piRNA binds to the piwi protein to form a piRNA-induced silencing complex (piRISC).[15] Processed piRISC is transported back in to the nucleus through nuclear pores where it inhibits the transcription of transposon elements.[16] Transposon elements have been identified to have a role in gene mutation leading to various diseases including cancers and infertility.[17,18]

Small Interfering RNAs (siRNAs)

Small interfering RNAs (siRNAs) are double-stranded, 21–25 nucleotide-long RNAs with two nucleotide overhangs at each hydroxylated 3′-end and phosphorylated 5′-end.[19] Once in the cytoplasm, RNAse III dicer enzyme cleaves the long double-stranded RNA into siRNA. The siRNA is incorporated into RISC, which consists of Argonaute (Ago) protein, Dicer, and transactivating response RNA-binding protein (TRBP), leading to separation of double-stranded siRNA into the sense and antisense strand within the RISC complex. The antisense strand, with more stable 5′-end, forms the activated RISC complex, which in turn, targets mRNA through complementary base pairing.[20–22]

Small Nucleolar RNA (snoRNA)

Small nucleolar RNAs (snoRNAs) are 60–300 base-pair-long unique RNAs found only inside the nucleolus. There are two types of snoRNAs: (1) C/D box containing snoRNAs and (2) H/ACA box containing snoRNAs.[23] Acting as a guide, snoRNAs direct selective chemical modification of nucleotides on other small housekeeping RNAs such as rRNAs. C/D box containing snoRNAs regulate sequence-specific 2′-O-methylation while H/ACA box snoRNAs regulate posttranscriptional isomerization of a uridine to a pseudouridine in rRNA.[24]

Circular RNAs (circRNAs)

Circular RNAs (circRNAs) are a large class of ncRNAs that originate from pre-mRNAs by a non-canonical splicing event called back-splicing. Consequently, loss of the terminal structures of a 5′-cap and a 3′-polyadenylation (poly-A) tail makes the circRNAs a covalently closed continuous ring structure.[25] The unique configuration of circRNAs confers protection from exonuclease-mediated degradation and makes them remarkably stable molecules.[4] Based on the sequence of origin, the circRNAs are categorized into exonic circRNAs (EcircRNA), intronic circRNAs (ciRNAs), exon-intronic circRNAs (ElciRNAs), intergenic circRNAs, and fusion circRNAs (f-cir-cRNAs). The EcircRNAs are the most abundant circRNAs predominantly located in the cytoplasm. The EcircRNAs function as miRNA sponge, modulate gene expression, regulate cell development and proliferation, as well as interact with RNA-binding proteins (RBPs).[26] CiRNAs and ElciRNAs are predominantly present in the nucleus and regulate transcription and translation.[27,28]

Advances in genetic technologies and bioinformatics have shown that circRNAs may be generated from intergenic, intronic, coding regions, as well as untranslated regions of the DNA. The biosynthesis of circRNAs is explained by three proposed models based on splicing event orders: (a) lariat-driven circularization, also known as exon-skipping model; (b) intron interaction-driven circularization, also known as the direct back-splicing model; and (c) re-splicing-driven circularization.[4,25] The biogenesis of circRNAs is illustrated in Fig. 2.

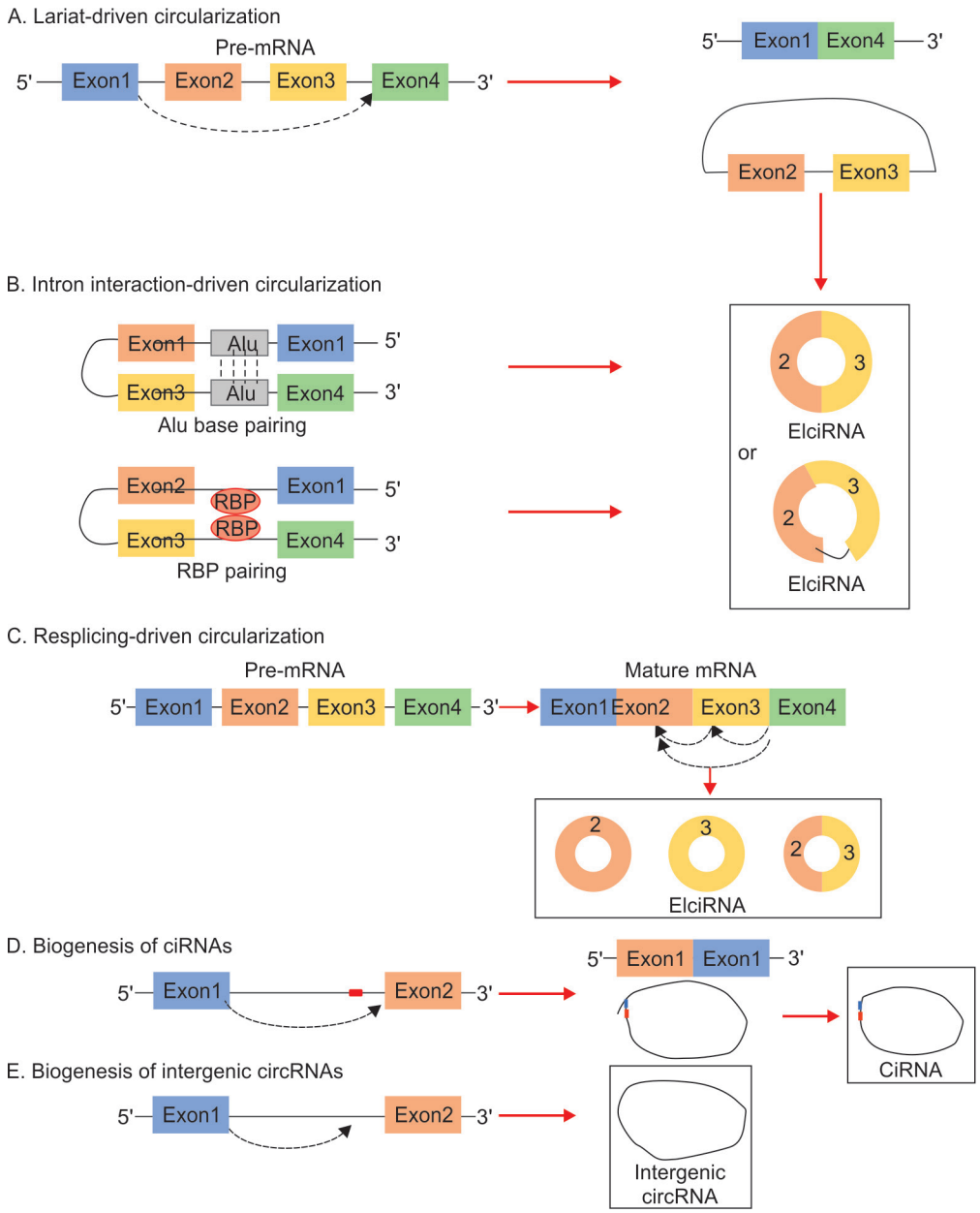
Long Non-coding RNAs (lncRNAs)

lncRNAs affect many cellular processes at transcriptional, posttranscriptional, and translational levels. Most lncRNAs are located within intergenic stretches and are usually comprised of two-exon transcripts.[29] These are interlaced, complex networks of overlapping sense and antisense transcripts that may also include protein-coding genes. Most ncRNAs, by definition, do not show protein-coding capacity, but some lncRNAs are now being identified to contain cryptic reading frames that may be translated into short, unstable micropeptides.[30] Some sequence elements in lncRNAs may show conserved structure, but these do not show conserved functions. In other regions, some lncRNAs that are derived from syntenic regions and presumably have shared evolution, no longer show any similarity in sequences.[31] These features suggest that many lncRNAs could possibly be non-functional or may have evolved from species-specific adaptive selection. The lncRNAs do seem to be important components of the address codes, which regulate directed trafficking, activation, and deactivation of protein complexes, genes, and chromosomes.[32]

Several types of lncRNAs have been identified. Based on proximity to the conventional protein-encoding mRNAs, lncRNAs can be classified as sense-, antisense-, or bidirectional lncRNAs.[33] Sense lncRNA regions may overlap one or more exons of another coding transcript. In other instances, antisense lncRNAs can extend into coding genes. LncRNAs have also been classified by the genomic location as intronic- or long intervening/intergenic-ncRNAs (lincRNAs). Intronic lncRNAs are encoded in non-coding DNA sequences.[34] The lincRNAs seem to be universal—these have been documented in plants, yeast, prokaryotes, and viruses, but the nucleotide sequences are not as well-conserved. Many lincRNAs are non-coding, autonomously transcribed long (>200 nucleotides) sequences that do not overlap with coding genes. Other classification group these into same-strand, isolated, convergent, or divergent categories, based on the location vis-à-vis the nearest protein-coding RNA.[35] In terms of function, lincRNAs may regulate cellular processes such as the p53-mediated transcriptional responses to DNA damage.[36]

ncRNA Associated with Prematurity that may Influence NEC

NEC is mainly a disease of premature neonates. Gestational age (GA) is inversely related to the incidence and severity of NEC. The intricate process of pregnancy maintenance and parturition necessitates a fine balance between many coordinated, consequential changes in hormones, tissue remodeling, metabolism, and immune system. Genetic factors, in conjugation with clinical and environmental variables, can alter the maternal-fetal interface and cause preterm birth. ncRNAs may play a regulatory role in gene expression controlling the process of pregnancy and birth. Since inflammation is a common theme for both, premature labor and NEC, various studies have evaluated miRNAs as well as lncRNAs that upregulate pro-inflammatory pathways and found that miRs-494, 142, 223, 15a, 329, 23a and lncRNAs-BF328678, BG258490, AA451649, BF667001, ENST00000423797, AX474492, BC107431, BX483760, DN918055,



Figs 2A to E: The biogenesis of circRNAs. (A) Lariat-driven circularization also known as exon skipping. Exon skipping during canonical splicing forms lariats containing the skipped exons as well as mRNAs. The exon-containing lariats undergo back-splicing yielding EcircRNAs (intronic sequence removed) or ElciRNAs (intronic sequence retained); (B) Intron interaction-driven circularization. Direct base pairing between cis-acting; splicing regulatory elements (Alu repeats) or trans-acting factors (RBPs) couples flanking introns, followed by back-splicing and exon circularization. (C) Resplicing-driven circularization. Exons on mature RNA can undergo back-splicing and produce EcircRNA; (D) Biogenesis of ciRNA. The GU-rich (near 5, splice site, blue box) and the C-rich (near 3, splice site, red box) sequences can escape the debranching and degradation and form ciRNAs; (E) Biogenesis of intergenic circRNAs

ENST00000437593 were associated with preterm labor (Luo 2013, Luo 2015).[37–42] Similarly, chorioamnionitis increases the risk of NEC in premature infants due to deleterious effect of chronic inflammation on fetal cell programming.[43] MiRNAs have been studied as modulators of chorioamnionitis, and consequently, its effects on fetal development and premature birth. Lee et al.[44] examined autopsy samples of fetuses exposed to chorioamnionitis and noted increased expression of miR-223-3p in fetal thymus (2.55-fold), lung (1.93-fold), and liver (1.7-fold). This is an important finding as thymus plays a critical role in T cell development and aberrant T-helper cell response may cause inflammation.[45,46] Montenegro et al.[47] evaluated miRNA expression with advancing gestation and with chorioamnionitis in 39 pregnant women. Compared to controls, pregnant women with preterm labor and chorioamnionitis had increased expression of miR-223 (37-fold) and miR-338 (24-fold). In another study, 48 Korean pregnant women with chorioamnionitis and preterm birth had decreased expression of miR-548, but increased HMGB1 and inflammatory cytokines.[48] These data

suggest a need for further study of ncRNAs in the pathogenesis of premature birth and neonatal morbidities.

Maternal preeclampsia is an important cause of preterm birth. Qian et al. noted increased expression of hsa_circRNA_100782, hsa_circRNA_102682, and hsa_circRNA_104820 in human placental tissues from mothers with preeclampsia.[49] Small for gestational age (SGA) neonates may be at increased risk of NEC.[50,51] Wang et al.[52] evaluated circRNAs in maternal and neonatal umbilical cord blood from SGA neonates and demonstrated that Hsa_circRNA15994-13, hsa_circ_0001359, and hsa_circ_0001360 were differentially expressed between SGA and AGA groups. The study also identified the target, hsa-miR-3619-5p, which plays an important role in the Wnt signaling pathway. These studies did not evaluate the neonatal outcomes, and future studies may be needed to examine neonatal outcomes.

ncRNAs Associated with Specific Histopathological Findings Seen in NEC

NEC is characterized by exaggerated inflammation, coagulative necrosis, and hemorrhagic necrosis.[1] In the following sections, ncRNAs that may be associated with the characteristic histopathological NEC features have been described.

ncRNAs Associated with Bowel Necrosis

The pathological process of NEC begins with intestinal epithelial cell (IEC) apoptosis, which results in mucosal defects and consequently, bacterial translocation from the gut lumen into the intestinal wall.[53–59] This triggers an overwhelming inflammatory response and mucosal necrosis, and can ultimately lead to NEC.[53,58,59] Apoptosis, programmed cell death, is immunologically a silent event, but NEC is characterized by exaggerated inflammation. To describe this unique pathoanatomical combination of NEC, a novel term, necroptosis, has been coined. Necroptosis may be caspase-independent in certain situations and can be triggered by death receptors such as transferrin-independent receptor-1 (NTFR1), interferon-production regulator (IFNR), Toll-like receptor (TLR) 3/4, Fas, and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). The ligation of death receptors activates the necrosome, a complex of the receptor-interacting serine/threonine kinases 1-3 (RIPK1-3) that in turn phosphorylates the mixed-linkage kinase domain-like protein (MLKL) to promote necroptosis.[60,61]

Werts et al.[62] examined IEC necroptosis and noted TLR-induced activation of RIPK1, RIPK3, and MLKL, and the protective effect of human breast milk. Li et al.[63] identified miR-141-3p as one of the agents that could possibly protect RIPK1 by downregulating RIPK1-MLKL-mediated necroptosis pathway. Chen et al.[64] identified motor neuron and pancreas homeobox (MNX) 1, also known as HB9 or HLXB9, as another binding target of miR-141-3p, by showing that it suppresses the MNX1 gene. MiR-141-3p may also alleviate inflammation, apoptosis, and oxidative stress damage by regulating MNX1 expression. Wu et al.[65] studied miR-431 in Chinese infants with stage 3 NEC (10 infants with NEC and an equal number of matched controls, and noted higher expression of miR-431 in the NEC group leading to suppressed forkhead box A1 (FOXA1) expression, and a significant effect downstream of miR-431-FOXA1 axis with exaggerated inflammation (increased expression of TNF, IL-6, IL-8, IL-10, NFKB2, and PLA2G2A), apoptosis (increased LGR5, decreased estrogen-related receptor gamma-ESRRG expression), and dysregulated tight junctions (decreased hepatocyte nuclear factor (HNF) 4A and PRKCZ expression). In another study, Ng et al.[66] searched for novel NEC biomarkers. After studying 301 episodes (36 episodes of NEC, 265 episodes of non-NEC) in Chinese infants, they identified three potential early biomarkers, miR-1290, miR-1246, and miR-375. MiR-1290 was most accurate in the detection of NEC (sensitivity of 0.83, specificity of 0.92, PPV of 0.6, and NPV of 0.98 with a cutoff of >220 copies/μL). When they combined miR-1290 level of >650 copies/μL measured on day 0 and CRP level of >15.8 mg/L measured on day 1, they were able to correctly recognize 30/36 (83%) NEC cases. MiR-1290 has been studied in colorectal cancer and inflammatory bowel diseases (IBDs) and is noted to modulate inflammation, cell renewal, and apoptosis via FOXA1 pathway.[67,68]

ncRNAs Associated with Intestinal Inflammation in NEC

NEC is marked by an acute inflammatory response to microbial invasion. However, the determinants of the severity of inflammation are not fully understood.[69] The pattern-recognition receptors (PRRs) are known to differentially recognize pathogens from other antigens and modulate the consequent immune responses. TLRs are one class of pattern-recognition receptors; TLR4 recognizes Gram-negative bacterial cell wall components such a lipopolysaccharide that may be involved in the pathogenesis of NEC. The activated TLRs recruit the myeloid differentiation (MD) factor and trigger downstream signaling to activate the nuclear factor-κB (NF-κB) and its related inflammatory responses.[70] Therefore, the role of ncRNAs in the regulation of TLR-mediated pathways may be important in NEC pathogenesis.

The role of miR-124 on TLR-mediated inflammation and apoptosis via myosin phosphate target subunit 1 (MYPT1) and rho-associated coiled-coil-containing protein kinase 1 (ROCK1) was evaluated by Yin et al.[71] using neonatal rat models of NEC. The study reported that miR-124 may protect against NEC by suppressing MYPT1, ROCK1, and TLR-9. Xu et al.[72] evaluated the regulatory interactions of miRNAs and lncRNAs in NEC pathogenesis. They reported upregulation of the lncRNA MSTRG.42950 and MSTRG.104993 and downregulation of lncRNAs MSTRG.61378 and MSTRG.8198. There are recognizable binding patterns: lncRNA MSTRG.42950 with miR181a-5p; lncRNA MSTRG.104993 with miR-124-3p; and miR-194-5p with lncRNA. MSTRG.61378 may bind miR-362-3p, and lncRNA MSTRG.8198 binds miR-124-3p. These interactions likely modulate the TLR4 signaling pathway, TORC2 complex, notch signaling pathway, the p53 signaling pathway, and the mTOR pathway and, consequently, determine the severity of inflammation in NEC. More recently, Sun et al. studied the role of let-7d-5p/LGALS3/TLR4/NF-κB axis in the inflammatory cascades known to be active in NEC lesions. They noted decreased let-7d-5p and increased LGALS3 (galectin) in such lesions, possibly pointing to anti-inflammatory and protective roles of let-7d-5p.

TLR pathways also activate macrophages, and these cells, in turn, control gene expression and immune response modulation. Ng et al.[73,74] evaluated the regulatory role of mcircRasGEF1B in the TLR4/LPS pathway. They identified increased mcircRASGEF1B in macrophages after LPS-induced activation. Depletion of mcircRasGEF1B dysregulated the TLR4/LPS pathway and caused macrophage dysfunction. Together, these findings provide future directions for large clinical studies with infants of different genetic backgrounds.

The nucleotide-binding oligomerization domain-containing (NOD) 2 is another cytosolic PRR that binds bacterial peptidoglycans and promotes pro-inflammatory cytokine production, inflammation, and innate immune defenses.[75] MiRNAs also interact with the NOD2 pathway in adults with IBD. MiRNAs including miR-122, miR-192,

miR-495, miR-671, miR-320, and miR-10a influence NOD2 expression, modulating inflammation and injury in IECs.[76–81] Such studies are needed to evaluate the role of these miRNAs in NEC.

Mannose-binding lectin (MBL) is a circulating PRR that opsonizes pathogens and activates the lectin pathway of the complement system. It is an important regulator of inflammation, in a variety of conditions such as neonatal sepsis, pneumonia, NEC, and IBD.[82–85] Prencipe et al. studied 107 neonates with NEC and showed that an SNP in the MBL2 gene increased serum levels of MBL in severe NEC.[86] MiRNA regulation of MBL levels has been previously examined in hepatocellular carcinoma; miR-942-3p has been noted to bind MBL2.[87] Studies are needed to evaluate how miRNAs may modulate the MBL pathway in NEC.

Pro-inflammatory cytokines are upregulated in NEC. The pathophysiological role of cytokines is unresolved; we still are unsure whether many of these cytokines are the cause, or the effect of inflammation in various conditions. Chen et al.[64] showed that increasing the expression of miR-141-3p can reverse the overexpression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α in intestinal injury models. In another study, Wu et al.[65] investigated miR-431 effects on TNF, IL-6, IL-8, and IL-10 and found it to increase IL-6 and TNF expression. Findings in these studies warrant future evaluation *in vivo* models and/or clinical studies in NEC.

ncRNAs Affecting Intestinal Microcirculation

Abnormalities in intestinal microcirculation due to maldevelopment or altered blood flow may contribute to NEC risk by causing intestinal ischemia and breach in mucosal integrity.[88] Vascular endothelial growth factor-A (VEGFA) plays a key role in intestinal vasculature development.[88,89] Association between decreased VEGF level and NEC has been established in both human as well as animal NEC models.[90] NcRNAs may regulate VEGFA genes affecting intestinal vasculature development and vasoreactivity.

The association between miRNAs modulating VEGF and NEC has been investigated. Liu et al.[91] reported downregulation of miR-429/200a/b and miR-141/200c clusters in four infants with NEC. The possible target genes for these two miRNA clusters, such as VEGFA, kinase insert domain receptor (KDR, also known as VEGFR2), FMS-related tyrosine kinase (FLT) 1, E-selectin (SELE), hepatocyte growth factor (HGF), were highly expressed in infants with NEC. Recently, these findings were confirmed by Zhao et al.[92] and also showed the interaction of miR-200c-3p and miR-22a-3p with KDR genes. The study identified three additional potential targets in apoptotic pathway, tyrosine 3-monooxygenase (TH)/tryptophan 5-monooxygenase activation protein gamma (YWHAG), YWHA protein epsilon (YWHAE), and YWHA protein beta (YWHAB).

Hypoxia is a main angiogenesis stimulus causing VEGF-mediated angiogenesis in endothelial cells. Fiedler et al.[93] identified two lncRNAs, LINC00323 and MIR503HG, in endothelial cells which are found to be highly sensitive to hypoxia and crucial for angiogenesis. Silencing of these two lncRNAs led to angiogenic defect, whereas endothelial cell treatment with VEGF increased their expression. Likewise, angiogenesis modulation by circRNAs has been explored in various pathological processes such as circ_100933, circ_100709, circ_104310 in infantile hemangioma;[94] circ_0004158, circ_0005768, circ_0008737, circ_0005324, circ_0007799, circ_0005477, circ_0000668, circ_0012698, circ_0013414 in retinopathy of prematurity;[95] circ_0005015, cZNF609, ZNF280c in diabetic retinopathy;[96] ZNF609, ZNF292, HIPK3, circ_0010729, circ_0003575, circ_0054633, antisense noncoding RNA in the INK4 locus (ANRIL), CPWWP2A, circ_0068087, circ_0008360, circ_0000109, circ_0002317 in cardiovascular diseases;[97] and SHKBP1, circ_002136 and SMARCA5 in tumorigenesis and metastasis.[98] Similar studies are needed in NEC examining the regulatory role of ncRNAs in intestinal angiogenesis.

ncRNAs Associated with Intestinal Hemorrhages in NEC

Clinical features of severe NEC commonly include coagulopathy and thrombocytopenia. There exists a knowledge gap explaining pathophysiology of coagulopathy and thrombocytopenia in NEC. The only available evidence is from a study by Giuliani et al.[99] who compared the expression of genes involved in coagulation in 11 infants with NEC with 22 controls and identified upregulation of hepatocyte growth factor (HGF), neutrophil-expressed elastase (ELANE), CD63, protein S (PROS1), and coagulation factor XII (F12) genes and downregulation of milk fat globule-EGF factor 8 (MFGE8), factor II (thrombin) receptor-like 1 (F2RL1), fibrinogen-like 2 (FGL2), plasminogen activator-tissue type (PLAT), protein C receptor (PROCR), serpin family D member 1 (SERPIND1), and hepatocyte nuclear factor-4a (HNF4A) genes. Out of these 12 genes, HNF4A is crucial for IEC maturation. Wu et al.[65] showed that overexpression of miR-432 inhibits in the Caco-2 cell model of NEC. However, the study did not highlight any effect on coagulation cascade and thrombocytopenia.

There is evidence to suggest the involvement of miRNAs in thrombocytopenia other neonatal inflammatory disorders. Cui et al.[100] identified a reduction in miR-130a expression in infants with sepsis who developed thrombocytopenia. MiR-130a targets IL-18 and/or IL-27 and was found to increase IL-18 expression without any change in IL-27 in the study. There has not been any study till date identifying specific ncRNAs associated with thrombocytopenia and coagulopathy in NEC providing an opportunity for future studies.

ncRNAs Associated with Gut Dysbiosis

Gut microbiome is a unique, complex interdependent ecosystem. With more than 3 million genes, gut microbiome can shape the gene expression in the host and determine health and diseases.[101] Dysbiosis is characterized by decreased diversity and overgrowth of pathogenic bacteria and has been linked to many inflammatory disorders, including NEC and IBD.[102] The microbiome development is a dynamic process that begins even before birth and undergoes dramatic changes during infancy due to vast contribution from various factors such as gestational age, mode of delivery, type of feeding, and antibiotic exposure.[103] Increasing information now associates genetics and the gut microbiome and *vice versa*.[104–106] Liang et al. studied conventional, germ-free, and gnotobiotic mice to characterize lncRNAs that are regulated by gut microbiota and identified six upregulated and overlapped lncRNAs, n26353, n290292, n297037, n294754, n264146, and n288632. Interestingly, most of them were highly expressed in spleen and thymus, suggesting the role of microbiome in immune modulation via lncRNAs. Dempsey et al.[107] demonstrated altered lncRNA expression in various organs such as the colon, liver, ileum, white fat tissue, jejunum, duodenum, and skeletal muscles. The mechanisms by which gut dysbiosis, lncRNA dysregulation, and intestinal inflammation may be linked need elucidation.

As mentioned earlier, miRNAs are the best-studied ncRNAs. These are more stable than other ncRNAs and are easier to measure in feces.[108–110] However, the fecal miRNA levels may be affected by the fecal microbiome.[108,111] The relationship between miRNA and gut dysbiosis has been studied in IBD and celiac disease. Mohan et al.

linked intestinal dysbiosis and altered claudin-1 expression/epithelial junctions with increased inflammation-related miRNAs, miR-203, miR-204, miR-23a, and miR-29b.[112] Studies in IBD have shown increased mir-144, mir-519, and mir-211, and downregulation of miR-577, miR-379-5p, miR-642-3p, and miR-26b-5p.[113,114] Similar studies are needed to examine the role of miRNAs in gut dysbiosis and NEC.

ncRNAs Associated with Protective Properties of Human Milk

Human breast milk, a biological "elixir," not only offers universally undisputed protection against NEC, but also reduces life-long health burden by preventing sudden infant death syndrome, bronchitis, lower respiratory tract infection, otitis media, atopy, and asthma.[115] Human breast milk contains a large spectrum of miRNAs, either as free molecules or carried in exosomes or extracellular vesicles (EVs), and is known to shape the gut microbiome.[116–120]

The influence of miRNAs in milk-derived exosomes on intestinal maturation and inflammation has been studied in the setting of IBD and NEC. The therapeutic effects of milk-derived exosomes have been studied in murine models of colitis and reported higher expression of miR-375, let-7z, miR-148, and miR-320 in milk as well as milk-derived exosome treated colon while lower expression of miR-125b in colitis. These miRNAs lower the expression of IL-1β, IL-3, IL-6, IL-12, IL-15, and TNF.[121–123] MiR-125b is known to regulate inflammation via NF-κB pathway that has a role in pathogenesis of NEC. MiR-148 also modulates immunity and has a role in metabolism and development. In intestinal cell culture models of NEC in rats and humans, milk-derived exosomes have shown a significant reduction in the incidence as well as the severity of NEC by anti-apoptotic, pro-proliferative, anti-inflammatory actions.[124,125] Future studies exploring the miRNA content of exosomes and comparing formula and breast milk content will shed some light on this innovative therapeutic option for NEC.

Many researchers have examined other ncRNAs in breast milk. Karlsson et al.[126] isolated 55 lncRNAs in EVs from human breast milk from 30 mothers within 2 months postpartum. These lncRNAs were present in more than 50% of the samples—CRNDE, DANCR, GAS5, HOTAIRM1, NCBP2-AS2, OIP5-AS1, PRKCQ-AS1, SNHG8, SRA1, TUG1, and ZFAS1. Later, Rubio et al.[127] first discovered the presence of more than 1,000 small RNAs in breast milk including piRNAs, tRNAs, snoRNAs, and snRNAs with tRNAs being the most abundant. Recently, studies have also examined lncRNAs and circRNAs in bovine as well as porcine milk-derived exosomes.[128,129] These data may be useful for future studies.

ncRNAs in IBDs in Adults

MiR-21 and miR-155 have been extensively studied in relation to IBD.[130–134] MiR-21, located on chromosome 17q23.2 in humans, regulates inflammation in the innate immune system. It directly targets the p35 subunit of Th1-promoting IL-12 and NOS in intestinal endothelial cells by modulating P13K/Akt signaling pathway encoding mRNA.[135] Increased miR-21 can alter the intestinal barrier and cause inflammation, oxidative stress, and cellular damage.[131,135] Similarly, miR-155, located on chromosome 21q21.3 in humans, induces IL-17 secreting helper T cells maturation process via IL-23/17/6 axis and has been implicated in the pathogenesis of IBD.[133,136–138] These findings are fascinating and provide future directions to confirm the role of miR-21 and miR-155 in neonates with NEC.

There is some information on the role of circRNAs and lncRNAs in IBD pathogenesis. Qiao et al.[139] profiled circRNAs and their targeted miRNAs, genes, and pathways in 13 patients with Crohn's disease (CD) and 13 controls; they found that hsa-circRNA-102685 may cause apoptosis via TLR and p53 signaling pathways via hsa-miR-146b-5p, hsa-miR-182-5p, and hsa-miR-146a-5p. Wang et al.[140] identified hsa_circRNA_0007919 disrupting mucosal integrity via miR-138 and hsa_let-7a after comparing differential expression of circRNAs between inflamed and non-inflamed intestinal mucosa from 30 patients with ulcerative colitis. Yin et al.[141] evaluated circRNAs in peripheral blood mononuclear cells obtained from IBD patients and discovered upregulation of hsa_circRNA_092520, hsa_circRNA_102610, hsa_circRNA_004662, and hsa_circRNA_103124, and correlation between circRNA_004662 and mTOR pathway via circRNA-miRNA-mRNA network prediction model. The mTOR plays a crucial role in the regulation of intestinal homeostasis and inflammation.[142] Autophagy-related 16-like 1 (ATG16L1), one of the autophagy-related genes (ATGs), is essential for maintaining immune homeostasis and may confer protection against NEC.[143,144] Genetic variation in ATG16L1 (Thr300Ala) increases risk of NEC, particularly in Caucasian infants.[145] Using animal model of IBD, Li et al.[146] showed that circRNA circPABPN1 blocked human antigen R (HuR) biding to atg16l1 mRNA and decreased ATG16L1 expression in the intestinal epithelium. Ye et al.[147] identified circRNA_103516 as a potential biomarker after showing upregulation of circRNA_103516 in 180 patients with IBD and associated downregulation of miR-19b-a-5p.

Similarly, lncRNAs can be viewed as novel potential biomarkers for diagnosis as well as promising therapeutic targets for intestinal inflammatory conditions such as IBD and NEC. LncRNAs such as lncRNA NEAT1 (nuclear paraspeckle assembly transcript 1), lncRNA H19, and lncRNA SPRy4-IT1 are essential for intestinal epithelial regeneration and repair, thus maintaining intestinal epithelial barrier function.[148] Studies have shown upregulation of lncRNA NEAT1 and lncRNA H19 in intestinal epithelium of IBD, whereas increased expression of lncRNA SPRy4-IT1 showed protective effect[149–151] by modulating barrier function. Similarly, several differentially expressed lncRNAs were potentially associated with intestinal mucosal immune homeostasis, function of pro-inflammatory cytokines, and MHC protein complex.[152] Specific inflammatory pathways affected by lncRNA dysregulation include those commonly identified in NEC pathogenesis such as NF-κB and TNF. Interleukin (IL)-1, IL-6, and IL-8 are often overexpressed in NEC and together with TNF; they stimulate NF-κB that leads to transcription of various inflammatory cytokines exacerbating the inflammation and tissue damage. Regulatory T lymphocytes (Tregs) are pivotal in keeping the excessive inflammation in check and maintenance of tolerance.[45] Qiao et al.[153] showed overexpression of lncRNA DQ786243 in 19 CD patients with active disease along with overexpression of cAMP response element binding protein (CREB) and forkhead box P3 (Foxp3), two key genes in function and development of Tregs, suggesting DQ786243, may be related to CD disease severity. Other lncRNA regulators of NF-κB have been implicated in the pathogenesis of IBD including lncRNA HIF1A-AS2, lncRNA ANRIL. Quan et al.[154] demonstrated inactivation of NF-κB/JNK pathway by lncRNA HIF1A-AS2 leading to decreased expression of cytokines IL-1β, IL-6, IL-12, and TNF-α in mice colon samples. Qiao et al.[155] demonstrated upregulation of lncRNA ANRIL in sigmoid colon mucosa obtained from 22 patients with UC and suggested that suppression of ANRIL may inhibit the development of UC by regulating miR-323-5p/TLR4/MyD88/ NF-κB pathway.

Conclusion

To expand our incomplete knowledge of complex NEC pathogenesis, we have reviewed the current literature on ncRNAs in NEC. The evidence remains imperfect due to scarcity of information on ncRNAs in NEC. Therefore, exploring the pathogenesis of other intestinal diseases such as IBD in adults and pediatric patients may provide a new direction to the future of NEC studies. Additionally, the complexity of NEC pathogenesis suggests that a single ncRNA may not explain NEC entirely. The evolution of high-throughput, in-depth next-generation sequencing techniques and bioinformatics may elucidate the interactions between different ncRNAs and their molecular mechanism in the pathogenesis of NEC.

Author Contribution

KD and JN wrote the manuscript. AM reviewed and made important revisions.

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