



MicroRNA: The Hidden Influencer of Embryo Quality

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Abstract

This article reviews the crucial roles of microRNAs (miRNAs) in embryo development and quality. It explains how miRNAs manage key developmental stages by regulating gene expression, epigenetic changes, and the way cells respond to oxidative stress. The review notes that proper miRNA function is vital for processes such as cell cycle progression, maintaining pluripotency, and tissue differentiation. When miRNAs do not function correctly, it can lead to developmental issues, improper epigenetic regulation, abnormal trophoblast development, and poor vascularization, all of which can ultimately affect embryo quality. Unique miRNA profiles have been found in high-quality embryos, indicating their potential as non-invasive markers for evaluating embryo competence in assisted reproductive technologies (ART). Highlighting the critical significance of miRNAs as well as the restrictions and difficulties in clinical applications of miRNAs related to reproductive biology, the article additionally addresses potential future uses of miRNAs and extracellular vesicles to improve embryo selection and outcomes in ART.

Keywords: miRNA; Embryos; Pluripotency; Epigenetic Modifications

Introduction

MicroRNAs (miRNAs) are small, non-coding RNA molecules that have emerged as key regulators of gene expression. These molecules, typically composed of 19 to 24 nucleotides, play a crucial role in various biological processes, including embryonic development. RNA polymerase Pol-II produces primary miRNA (pri-miRNA) to start canonical miRNA production. Drosha and Dicer are two ribonucleases that act sequentially to convert pri-miRNA into an RNA duplex of around 22 nucleotides. When the duplex is loaded onto an Ago protein, it generates an effector complex called the RNA-induced silencing complex (RISC), which removes one strand. Non-canonical biogenesis pathways may generate miRNAs via alternative mechanisms that do not involve Drosha or Dicer [1]. Embryo development is a highly intricate and precisely

controlled process that encompasses a series of crucial events, ultimately leading to the formation of a fully functional organism. This developmental journey begins with fertilization, followed by cleavage, blastulation, gastrulation, and, ultimately, organogenesis. Any disruptions or aberrations during these pivotal stages can result in developmental disorders or infertility. Recently, miRNAs have emerged as essential players in orchestrating the delicate balance necessary for successful embryogenesis [2]. miRNAs primarily exert their influence through post-transcriptional regulation. They bind to the 3' untranslated region (UTR) of target messenger RNAs (mRNAs), leading to translational repression or mRNA degradation [3]. This mode of action enables miRNAs to fine-tune the expression of a broad range of genes, often coordinating entire genetic networks. The significance of miRNAs in embryonic development

becomes apparent when considering that a single miRNA can target multiple genes, making them potent regulators of complex developmental processes [4]. Research has unveiled a wealth of insights into the specific roles of miRNAs in embryo development. In zebrafish embryogenesis, the miR-430 family plays a crucial role in regulating maternal mRNA clearance during the maternal-to-zygotic transition [5].

In mammals, members of the miR-290 cluster have been linked to pluripotency and the early development of embryonic stem cells [6]. Additionally, miR-21 expression is essential for the development of human oocytes, making it a potential biomarker for oocyte maturity. Elevated levels of miR-21 were found in PCOS conditions in the follicular fluid, and granulosa cells are associated with regulating the expression of genes that influence oocyte maturation and early embryo development [7]. Furthermore, miR-21 shows promise as a diagnostic marker for oocyte maturity and embryo quality in females undergoing intracytoplasmic sperm injection (ICSI). Research has revealed promising correlations between miR-21 expression levels and oocyte and embryo quality, providing a valuable addition to the growing body of miRNA research in the field of ART [8]. Recent studies have highlighted miR-125a as a crucial regulator of blastocyst implantation in mice, targeting genes involved in trophoblast invasion [9]. Furthermore, miR-34 family members have been implicated in controlling the balance between self-renewal and differentiation in developing embryos [10].

Moreover, miRNAs are known to play crucial roles in stem cell maintenance and differentiation, which are fundamental processes in embryonic development. miR-145 has been identified as a regulator of embryonic stem cell differentiation by targeting key pluripotency factors such as *OCT4* and *SOX2*. By promoting differentiation, miR-145 contributes to the formation of specialized cell types [10]. Additionally, miRNAs intersect with important developmental pathways like the transforming growth factor-beta (TGF- β) signaling pathway, which is critical in embryogenesis. miR-24 acts as a negative regulator of TGF- β signaling by targeting the TGF- β receptor, illustrating the intricate interplay between miRNAs and crucial developmental

signaling pathways [11]. miRNAs serve as hidden influencers of embryo quality and development. miR-200c regulates TGF- β signaling in human embryos, influencing the epithelial-to-mesenchymal transition during gastrulation [12]. Their ability to finely tune gene expression, regulate developmental pathways, and control stem cell differentiation makes them important molecules in embryogenesis.

The crucial role of miRNA in embryonic development

Embryo development is a dynamic process marked by a series of sequential events, including fertilization, cleavage, blastulation, gastrulation, and organogenesis (Table 1). Each of these stages is carefully regulated by a network of molecular signals, among which miRNAs have emerged as crucial regulators. miRNAs play a pivotal role in this process by regulating key events such as preventing poly-spermy, modulating cell cycle progression, and initiating zygotic genome activation (ZGA) [13]. miR-34c has been identified as a key player in preventing polyspermy by regulating the expression of multiple sperm-binding proteins [14]. Additionally, miRNAs like the miR-290 cluster members are involved in regulating the G1/S transition during early cleavage stages, ensuring proper cell cycle progression [15]. Furthermore, miRNAs are essential for initiating ZGA, ensuring the timely activation of embryonic genes for subsequent developmental processes [16]. During blastulation, the embryo undergoes rapid cell divisions, leading to the formation of the blastocyst. miRNAs are crucial in coordinating these processes by modulating cell fate decisions, cell proliferation, and lineage specification. miR-34a has been implicated in regulating the balance between self-renewal and differentiation in embryonic stem cells, thus influencing lineage commitment [17]. Moreover, miRNAs such as the miR-302/367 cluster are vital for maintaining pluripotency and regulating the transition from the inner cell mass to the trophectoderm lineage [18]. New evidence indicates that miR-372 promotes blastocyst formation in human embryos by upregulating cell adhesion molecules [19]. Gastrulation marks a critical phase in embryo development, during which three primary germ layers [ectoderm, mesoderm, and endoderm] are established. miRNAs are central players in this process, coordinating cell fate determination and tissue patterning. miR-430, a highly conserved miRNA in vertebrates, has been shown to regulate the transition from pluripotency to -

differentiation by targeting pluripotency factors during zebrafish gastrulation [5]. miRNAs play an indispensable role in regulating the expression of key developmental genes, ensuring proper organ formation. miR-196a has been implicated in regulating Hox genes, which are master regulators of body axis patterning and organogenesis [20]. miRNAs like the miR-17-92 cluster are

crucial for heart development, controlling cardiomyocyte proliferation and differentiation [21]. The importance of miRNAs in embryo development underscores their essential role in the complex series of events leading to the formation of a functional organism. miR-133a has been recently implicated in neural crest development, modulating neuronal differentiation in mouse embryos [22].

Table 1: Role of miRNAs at different developmental stages.

Embryonic stage	miRNA[s]	Function
Fertilization	miR-34c	Prevents polyspermy [14]
Cleavage	miR-290 cluster	Regulates G1/S transition and cell cycle progression, promotes cell division, prepares for zygotic genome activation (ZGA) [15]
Blastulation	miR-34a	Balances between self-renewal and differentiation [17]
	miR-302/367 cluster	Influences stem cell fate [18]
Gastrulation	miR-430	Transition from pluripotency to differentiation, target pluripotency factors [5]
	miR-372	Promotes blastocyst formation, upregulates cell adhesion molecules [19]
Organogenesis	miR-196a	Regulates Hox genes, cardiomyocyte proliferation, and heart development [20]
	miR-17-92	Neural crest development, neuronal differentiation [21]

Mechanisms of miRNA regulation in embryo quality

Embryo quality is a critical determinant of successful pregnancy outcomes in assisted reproductive technologies (ART). It encompasses various factors, including developmental stage, morphological characteristics, and genetic integrity. miRNAs function as post-transcriptional regulators, allowing for precise control over gene expression. The binding mechanism of miRNA to the 3' UTR is crucial for maintaining the delicate balance of gene expression required for proper embryo development [23]. miR-21 has been implicated in the regulation of genes involved in apoptosis and cell cycle progression, thus influencing embryo quality [24]. miRNAs also play a pivotal role in epigenetic regulation by targeting genes associated with chromatin modification and DNA methylation. Members of the miR-29 family have been shown to target DNA methyltransferases (DNMTs), thereby influencing DNA methylation patterns that are essential for normal embryo development [25]. Other miRNAs, like miR-140, have been identified as novel regulators of histone acetylation in human embryos, promoting proper chromatin remodeling [26]. This epigenetic modulation is essential for establishing the appropriate epigenetic landscape required for cellular differentiation and tissue development. Proper

cell cycle progression is a cornerstone of embryo quality. miRNAs serve as key players in this process, ensuring precise control of cell cycle checkpoints. Dysregulation of miRNAs involved in cell cycle regulation can lead to aberrant proliferation or differentiation, thereby compromising embryo quality. miRNAs are central to maintaining pluripotency and orchestrating lineage commitment.

Oxidative stress, which can lead to DNA damage and cellular malfunction, may negatively impact the quality of the embryo. The cellular response to oxidative stress is partially regulated by miRNAs. Embryos defend against oxidative damage through miR-210, identified as a critical regulator of the hypoxic response [27]. Recently, miR-155 has been found to alleviate oxidative stress in porcine embryos by targeting antioxidant enzymes [28]. Dysregulation of miRNAs involved in oxidative stress response pathways can adversely affect embryo quality. Maternal factors, including environment-based miRNAs, can also influence embryo quality. Early developmental processes are governed by maternal miRNAs, which are transferred from the mother to the developing embryo. It has been shown that the abundantly present miR-30d regulates early embryonic development [29]. To fully grasp the

broader regulatory network controlling embryo quality, it is essential to understand the dynamics of maternal-embryonic miRNA interaction.

Impact of miRNA dysregulation on embryo quality

Dysregulation of specific miRNAs can lead to altered differentiation patterns and disrupted cell fate decisions during embryonic development. Aberrant expression of miR-34a has been associated with the perturbed differentiation of neural progenitor cells, potentially causing abnormalities in neural tissue development [30]. This indicates that miRNA dysregulation can result in developmental anomalies affecting embryo quality. miRNAs influence epigenetic regulation by targeting genes involved in chromatin remodeling and DNA modification. Dysregulated miRNA expression can result in improper epigenetic modifications, affecting gene expression profiles that are critical for normal embryonic development. Members of the miR-29 family have been shown to target histone deacetylases, influencing histone acetylation levels and potentially leading to altered gene expression patterns [31]. Disruptions in epigenetic regulation can lead to aberrant differentiation and compromised embryo quality. Dysregulation of miRNAs can significantly impact trophoblast development, a crucial event in early embryogenesis. Proper trophoblast differentiation is essential for establishing a functional placenta. miR-34c has been implicated in regulating trophoblast proliferation and differentiation, suggesting that its dysregulation can result in abnormalities in placental development [32]. Altered trophoblast development can have cascading effects on embryonic growth and overall quality.

Proper vascularization is essential for supplying nutrients and oxygen to developing embryos. Abnormalities in miRNAs involved in angiogenesis and vascular development can lead to impaired blood flow and nutrient delivery. miR-126 has been identified as a key regulator of vascular integrity, and its dysregulation can lead to vascular abnormalities that affect embryo quality [33]. Dysregulation of miR-199a has been linked to defective angiogenesis in human embryos, compromising placental vascularization [34]. Environmental factors, such as maternal nutrition and exposure to toxins, can modulate miRNA expression levels, contributing to miRNA dysregulation. These environmental influences can directly affect embryo quality, i.e., maternal exposure to a high-fat diet

has been shown to alter miRNA expression patterns in oocytes, potentially influencing early embryonic development [35]. Understanding the interplay between environmental factors and miRNA dysregulation is crucial for comprehending the broader regulatory network guiding embryo quality. miRNAs play a significant role in regulating mitochondrial function and metabolic homeostasis, both of which are vital for embryonic development. miR-181a has been implicated in regulating mitochondrial function, and its dysregulation can lead to mitochondrial dysfunction in developing embryos [36]. Impaired mitochondrial function can detrimentally affect embryonic development and overall quality.

miRNA profiles in high quality embryos

Recent studies have unveiled specific miRNA signatures that distinguish high-quality embryos from their lower-quality counterparts. miR-302b-3p and miR-512-3p are identified as significantly upregulated in high-quality embryos [37]. These miRNAs are predicted to target genes associated with cellular proliferation and differentiation, which may enhance the developmental competence of high-quality embryos. Beyond miRNA profiles, recent research has illuminated the intricate interactions between different classes of non-coding RNAs within high-quality embryos. Specifically, long non-coding RNAs (lncRNAs) have been shown to act as competing endogenous RNAs (ceRNAs) for miRNAs, thereby modulating miRNA activity and gene expression. This regulatory network involving lncRNAs and miRNAs contributes to the precision of gene expression in high-quality embryos [38]. Metabolic regulation is crucial for embryonic development, and miRNAs play a role in maintaining metabolic homeostasis in high-quality embryos. miR-210 has been identified as a key regulator of mitochondrial function and metabolism, with its upregulation in high-quality embryos enhancing energy production to provide the necessary resources for successful development [39]. The transition from maternal control to zygotic control of embryonic development is a critical phase marked by dynamic changes in miRNA expression patterns. Research has identified miR-371a-3p as a maternally inherited miRNA that exhibits a sharp decline during this transition, while zygotically expressed miRNAs, such as miR-151a-3p, become increasingly prominent [40]. Understanding this transition is essential for comprehending the regulatory shifts in early embryonic development. Beyond their roles as regulators, miRNAs and other non-coding RNAs

have emerged as potential therapeutic targets in the context of improving embryo quality. Strategies involving the modulation of specific miRNAs or lncRNAs to enhance developmental competence are actively being explored. These approaches hold promise for improving ART outcomes and addressing infertility issues [38]. Understanding the miRNA profiles associated with high-quality embryos is essential for optimizing ART procedures and advancing our knowledge of early embryonic development. Recent research has uncovered distinctive miRNA signatures, highlighted non-coding RNA interactions, emphasized epigenetic control, and underscored the role of miRNAs in metabolic regulation. Furthermore, insights into the maternal-to-zygotic transition and the potential of non-coding RNA-based therapeutics have expanded our understanding of embryo quality.

Future prospects: advancing embryo quality assessment with miRNA

The potential of microfluidics in isolating and characterizing extracellular vesicles (EVs) for standardized assessment of embryo quality is highlighted in a previous study [41]. This study highlights the significance of EVs in providing valuable insights into the microenvironment surrounding the embryo, potentially offering a non-invasive and reliable method for evaluating embryo quality. It discusses the role of miRNA-21 in regulating the viability of cumulus cells, which are critical for supporting oocyte development. The study suggests that miRNA-21 may influence the developmental potential of the oocyte by modulating the function of cumulus cells. This finding holds promise for utilizing miRNA-21 as a potential marker for assessing embryo quality [42]. Additionally, it examines miR-532-3p in cumulus cells of infertile females with advanced endometriosis. The study highlights miR-532-3p as a potentially altered miRNA in these cells, indicating its significance in the context of compromised fertility. This research provides insights into specific miRNAs that may indicate altered embryo quality in certain clinical conditions [43]. Past studies have presented a systematic review and meta-analysis focused on miRNAs in male infertility. While the study primarily addresses male infertility, it underscores the broader potential of miRNAs as diagnostic markers in reproductive medicine [44]. The findings suggest that miRNAs may offer a non-invasive and

accurate means of diagnosing male infertility, which could have implications for embryo selection in IVF. Previous research underscores the significance of EVs, including their miRNA cargo, in mediating intercellular communication during various reproductive processes [45]. Recently, it was demonstrated that miR-146a in EVs from follicular fluid predicts embryo implantation success in IVF, offering a non-invasive biomarker [46]. Understanding the role of EVs in embryo quality assessment could lead to innovative approaches in ART. The findings from these research articles collectively highlight the potential of miRNAs in advancing embryo quality assessment. By leveraging miRNAs as biomarkers, clinicians may enhance the accuracy of embryo selection in ART procedures, ultimately improving pregnancy outcomes for patients undergoing IVF. Furthermore, the integration of EVs and their miRNA cargo into embryo quality assessment provides an exciting avenue for non-invasive evaluation. This approach could reduce the need for invasive procedures and mitigate potential harm to developing embryos, leading to safer and more ethical practices in ART. The incorporation of miRNAs into embryo quality assessment represents a promising advancement in the field of assisted reproductive technologies. As demonstrated by several research articles, miRNAs have the potential to be valuable biomarkers for evaluating embryonic competence.

Future research should focus on investigating specific miRNAs and EVs that are essential for embryo development. Additionally, efforts should be directed toward establishing standardized protocols for miRNA analysis and validating miRNA-based embryo selection methods through large-scale clinical trials.

Conclusion

A significant turning point in the field of assisted reproduction is the expanding research on microRNAs in relation to assessing embryo quality. The studies discussed here collectively highlight the potential of miRNAs as valuable biomarkers for enhancing the success rates of in vitro fertilization. However, it is crucial to approach this promising research avenue with methodological rigor and a focus on quality over quantity. As this review reveals the complexities of miRNA-mediated regulation in reproductive processes, we get closer to a future where ART outcomes are further improved, providing new insights into the field of breeding.

Conflict of Interest

Authors have no conflict of interest.

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