Journal of Bioscience and Environment Research 2 (1): 1-3

Content available at Genesis Publishing Consortium Limited

Journal of Bioscience and Environment Research

Journal homepage: www.genesispcl.com/journals/jber

Editorial

The gradual discovery of cell-type and context specificity of microRNAs

Khokon Kumar Dutta *

Department of Biochemistry and Molecular Biology, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj-8100, Dhaka, Bangladesh

Article info

Article history
Received: 18 October 2024
Revised: 08 November 2024
Accepted: 10 November 2024
Published: 15 November 2024

Keywords
microRNA
Tissue-specific microRNAs
Cell-type-specific microRNAs
Context-specific microRNAs
Environment-specific microRNAs

Abstract

The discovery of microRNAs (miRNAs) has revolutionized our understanding of gene regulation, particularly through their cell-type and context-specific functions. This perspective explores the gradual realization of miRNA specificity, beginning with the identification of *lin-4* in *Caenorhabditis elegans* and progressing to the discovery of tissue-specific miRNAs such as miR-122 in the liver and miR-1 in muscle. A central focus is miR-34a, one of the most studied miRNAs, which exemplifies the importance of cellular context in miRNA function. miR-34a's role in tumor suppression via the p53 pathway, demonstrating that its ability to induce apoptosis and cell cycle arrest depends on the cellular environment. miR-34a overexpression can have diverse effects on cell proliferation, ranging from strong suppression in certain cell types to minimal or paradoxical responses in others. In situ analysis of rat tissues revealed tissue-specific expression of miR-34a, with high levels in cerebral neurons and Purkinje cells and faint expression in renal, hepatic, and myocardial tissues. These findings suggest that miR-34a plays distinct roles depending on the tissue, contributing to homeostasis in some contexts while exhibiting a lesser regulatory role in others. This review synthesizes key studies that underscore the critical role of miRNAs, such as miR-34a, in regulating gene expression in a tissue and context-specific manner, providing insights into both normal physiology and disease pathogenesis.

Since their discovery in the early 1990s, microRNAs (miRNAs) have emerged as pivotal regulators of gene expression, influencing a wide range of biological processes. Early studies focused on understanding the general regulatory functions of miRNAs, but subsequent research has revealed their intricate cell-type and context-specific roles. This gradual process of discovery has unveiled the complexity of miRNA regulation and their functional specificity, contributing significantly to our understanding of development, disease, and tissue-specific regulation.

The journey of miRNA research began with the landmark discovery of *lin-4* in *Caenorhabditis elegans* by Lee *et al.* (1993). This small RNA was found to regulate the *lin-14* gene, introducing the world to miRNAs. However, it was not until subsequent studies that the tissue-specific roles of these molecules were revealed.

A major breakthrough in tissue-specific miRNA expression came with the identification of miR-122 as a liver-specific miRNA by Lagos-Quintana *et al.* (2002). This finding linked miRNAs to organ-specific functions, shedding light on their role in tissue homeostasis and metabolic regulation. Subsequently, the identification of miR-1 as muscle-specific highlighted the importance of miRNAs in organ development, particularly in muscle differentiation and growth (Chen *et al.*, 2006).

These early discoveries were crucial in shifting the focus of miRNA in different tissues. The realization that miRNAs could have distinct expression patterns depending on the tissue or organ marked the beginning of the concept of miRNA specificity in biological systems.

Corresponding authors
Email address: kkdutta@bsmrstu.edu.bd (Khokon Kumar Dutta)

doi: https://doi.org/10.69517/jber.2024.02.01.0001

One of the most studied miRNAs, miR-34a, exemplifies the importance of cellular context in miRNA function. Its role in tumor suppression, particularly through the p53 pathway, was demonstrated in a seminal paper by He *et al.* (2007). The study showed that miR-34a could induce apoptosis and cell cycle arrest, but these effects were dependent on the cellular context. miR-34a's ability to mediate different outcomes based on the cell type it operates in underscores the complexity of miRNA regulation.

The context-dependent nature of miR-34a activity was further underscored by Dutta *et al.* (2007). We demonstrated that miR-34a overexpression could elicit diverse effects on cellular proliferation, depending on the cell type. Our research revealed that miR-34a, a well-established tumor suppressor, exerts variable influences on cell growth. In certain contexts, miR-34a inhibits proliferation by down regulating targets involved in cell cycle regulation and apoptosis. However, the study revealed that miR-34a overexpression does not universally suppress cell growth. In specific cell types, the response was minimal or even paradoxical, suggesting that miR-34a's effects are intricately tied to the cellular environment.

Dutta *et al.* (2007) also conducted an *in situ* analysis of healthy rat tissues, providing additional evidence for the tissue-specific expression of miR-34a. They observed significant variations in miR-34a levels across different tissues, with cerebral neurons and Purkinje cells exhibiting the highest expression. In contrast, normal renal tubules, hepatocytes, and myocardial cells showed faint expression. This differential expression suggests that miR-34a plays distinct functional roles depending on the tissue type. In tissues where miR-34a is highly expressed, it may be involved in maintaining homeostasis by regulating cell turnover. Conversely, in tissues with lower miR-34a expression, its regulatory role might be less pronounced. These findings reinforce the notion that miR-34a's effects on cellular processes, including proliferation and cell cycle regulation, are intricately linked to the local cellular context.

The development of next-generation sequencing technologies has revolutionized miRNA research, enabling large-scale studies to catalog miRNA expression across different tissues and cell types. The creation of a mammalian miRNA expression atlas by Landgraf *et al.* (2007) provided a comprehensive overview of miRNA expression patterns, further supporting the concept of cell-type specificity. By cataloging miRNA expression in a wide range of mammalian tissues, this study highlighted that miRNAs are not only tissue-specific but also highly regulated depending on the cellular environment. This atlas laid the groundwork for understanding miRNA function in a broader, more systemic context.

In addition, studies such as that by Lim *et al.* (2005), demonstrated that miRNAs could regulate large numbers of target mRNAs in specific tissues. This large-scale regulation highlights the potential of miRNAs to fine-tune gene expression in a context-dependent manner, exerting significant control over cellular processes such as differentiation, metabolism, and apoptosis.

Beyond tissue specificity, miRNAs also play critical roles in developmental and disease-specific contexts. For example, the miRNAs miR-1 and miR-133 have been shown to be essential in cardiovascular development and muscle differentiation (Chen *et al.*, 2006; Zhao *et al.*, 2007). Their context-specific roles in heart and skeletal muscle highlight how miRNAs can regulate tissue-specific developmental processes. Similarly, miR-29 has been found to modulate p53 activity in a context-dependent manner, depending on the cellular environment, as demonstrated by Park *et al.* (2009).

These findings emphasize that miRNA function cannot be generalized across all cells; rather, their effects are shaped by the intricate interactions within specific cellular and developmental contexts. This context specificity is crucial for maintaining normal physiological function and for understanding the aberrant regulation of miRNAs in diseases like cancer.

The discovery of cell-type and context specificity of miRNAs has been a transformative process in molecular biology. From the initial identification of miRNAs to the realization of their specialized functions in different tissues and cell types, research has revealed that miRNA regulation is highly context-dependent. Studies on miRNAs like miR-34a, miR-122, and miR-1 have underscored the importance of the cellular environment in determining miRNA function. As the field continues to evolve, further exploration of miRNA specificity will undoubtedly uncover new layers of complexity, particularly in understanding diseases and developing targeted therapies. The challenge ahead lies in unraveling how miRNAs interact with diverse cellular networks to maintain homeostasis and how their dysregulation contributes to disease.

Declaration by author

The authors declare that the manuscript was generated with the assistance of ChatGPT, an artificial intelligence program developed by OpenAI. However, the authors are responsible for the content and accuracy of the manuscript.

Acknowledgments

The author would like to express his sincere gratitude to Professor Shinya Toyokuni, MD, PhD, Kyoto University (present location, Nagoya University), Japan, for supporting, guiding, and supervising the discovery of cell-type and context specificity of microRNA-34a.

Ethical approval statement

None to declare.

Data availability

Not applicable.

Informed consent statement

Not applicable.

Conflict of interest

The author declare no competing interests.

Authors' contribution

Khokon Kumar Dutta contributed to the design and writing of this editorial.

References

Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM, Conlon FL and Wang DZ, 2006. The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. Nature Genetics, 38 (2): 228-233. http://doi.org/10.1038/ng1725

Dutta KK, Zhong Y, Liu YT, Yamada T, Akatsuka S, Hu Q, Yoshihara M, Ohara H, Takehashi M, Shinohara T, Masutani H, Onuki J and Toyokuni S, 2007. Association of microRNA-34a overexpression with proliferation is cell type dependent. Cancer Science, 98: 1845–1852. https://doi.org/10.1111/j.1349-7006.2007.00619.x

He L, He X, Lim L, de Stanchina E, Xuan Z, Liang Y, Xue W, Zender L, Magnus J, Ridzon D, Jackson AL, Linsley PS, Chen C, Lowe SW, Cleary MA and Hannon GJ, 2007. A microRNA component of the p53 tumour suppressor network. Nature, 447: 1130–1134. https://doi.org/10.1038/nature05939

Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W and Tuschl T, 2002. Identification of tissue-specific microRNAs from mouse. Current Biology, 12 (9): 735-739. http://doi.org/10.1016/s0960-9822(02)00809-6

Landgraf P, Rusu M, Sheridan R, Sewer A, Iovino N, Aravin A, Pfeffer S, Rice A, Kamphorst AO, Landthaler M, Lin C, Socci ND, Hermida L, Fulci V, Chiaretti S, Foà R, Schliwka J, Fuchs U, Novosel A, Müller RU, Schermer B, Bissels U, Inman J, Phan Q, Chien M, Weir DB, Choksi R, De Vita G, Frezzetti D, Trompeter HI, Hornung V, Teng G, Hartmann G, Palkovits M, Di Lauro R, Wernet P, Macino G, Rogler CE, Nagle JW, Ju J, Papavasiliou FN, Benzing T, Lichter P, Tam W, Brownstein MJ, Bosio A, Borkhardt A, Russo JJ, Sander C, Zavolan M and Tuschl T, 2007. A mammalian microRNA expression atlas based on small RNA library sequencing. Cell, 129 (7): 1401-1414. http://doi.org/10.1016/j.cell.2007.04.040

Lee RC, Feinbaum RL and Ambros V, 1993. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. Cell, 75 (5): 843-854. http://doi.org/10.1016/0092-8674(93)90529-Y

Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS and Johnson JM, 2005. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature, 433 (7027): 769-773. http://doi.org/10.1038/nature03315

Park SY, Lee JH, Ha M, Nam JW and Kim VN, 2009. miR-29 miRNAs activate p53 by targeting p85 alpha and CDC42. Nature Structural and Molecular Biology, 16: 23-29. http://doi.org/10.1038/nsmb.1533

Zhao Y, Ransom JF, Li A, Vedantham V, von Drehle M, Muth AN, Tsuchihashi T, McManus MT, Schwartz RJ and Srivastava D, 2007. Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. Cell, 129 (2): 303-317. http://doi.org/10.1016/j.cell.2007.03.030