—Review—

Perioperative Anesthesia Management: The Role of MicroRNAs

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MicroRNA (miRNA) is a small RNA molecule that does not code for proteins, and organ- and disease-specific miRNAs are being investigated as diagnostic tools and therapeutic targets, particularly for cardiovascular disease and cancer. Much remains unknown about how anesthetics, other drugs, and perioperative management affect miRNAs, but miRNA-targeted drugs might eventually be used perioperatively. This review examines changes in miRNA expression related to anesthesia management. Sevoflurane results in gene expression patterns that differ by organ. The author investigated changes in miRNA expression induced by anesthetics in the brain, lungs, and liver and found that changes in miRNA expression differ by drug and organ. Since miRNA does not have a one-to-one correspondence with its target mRNA and exhibits complex effects within and between cells, as well as remotely, drug- and organ-specific changes in mRNA expression caused by anesthetics likely involve complex alterations. Cardiovascular disease and cancer are related to perioperative management via miRNAs. Inhalational anesthetics may exacerbate or suppress cellular activity, depending on the type of cancer, and the mechanisms of action differ depending on the inhalational anesthetic. These findings suggest that propofol is more likely to contribute to suppression of cancer cells through intercellular communication. The role of miRNA in perioperative management remains unclear. In the future, it is expected that changes in miRNA expression will be considered when selecting and administering anesthetic drugs perioperatively. (J Nippon Med Sch 2025; 92: 14–21)

Key words: anesthesia, microRNA, cancer, cardiovascular surgery

Introduction

The global increase in surgical procedures highlights the crucial role of anesthesiologists. Surgery remains the primary treatment worldwide for solid tumors, and more than 60% of cancer patients require general anesthesia for their initial surgical procedures[1]. Postoperative mortality is the third leading cause of death, after cardiovascular disease and stroke, and accounts for 7.7% of deaths worldwide[2]. Surgical stress triggers neural and inflammatory cellular signaling, which can influence postoperative complications. Anesthetics may also pose a risk because of their direct immunomodulatory effects and effects on cellular signaling pathways. The underlying molecular mechanisms responsible for these clinical findings have not been comprehensively explored.

MicroRNA (miRNA) is a small RNA molecule that does not code for proteins and was first discovered in *C. elegans* in 1993[3]. Subsequent research identified organ- and disease-specific miRNAs, which are being investigated as diagnostic tools and therapeutic targets, particularly for cardiovascular disease and cancer[4–6]. As of September 2024, there have been 173,216 published papers on miRNA. However, the first report on miRNA in the field of anesthesia was published in Japan in 2007[7], and there are currently 2,792 reports, indicating that research in this area is still developing. Although much remains unknown about how anesthetics, other drugs, and perioperative management affect miRNAs, it is anticipated that miRNA-targeted drugs will be used perioperatively in the future. This review examines changes in miRNA expression related to anesthesia management.

MicroRNAs

The traditional central dogma held that genetic informa-

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https://doi.org/10.1272/jnms.JNMS.2025_92-116
Journal Website (https://www.nms.ac.jp/sh/jnms/)

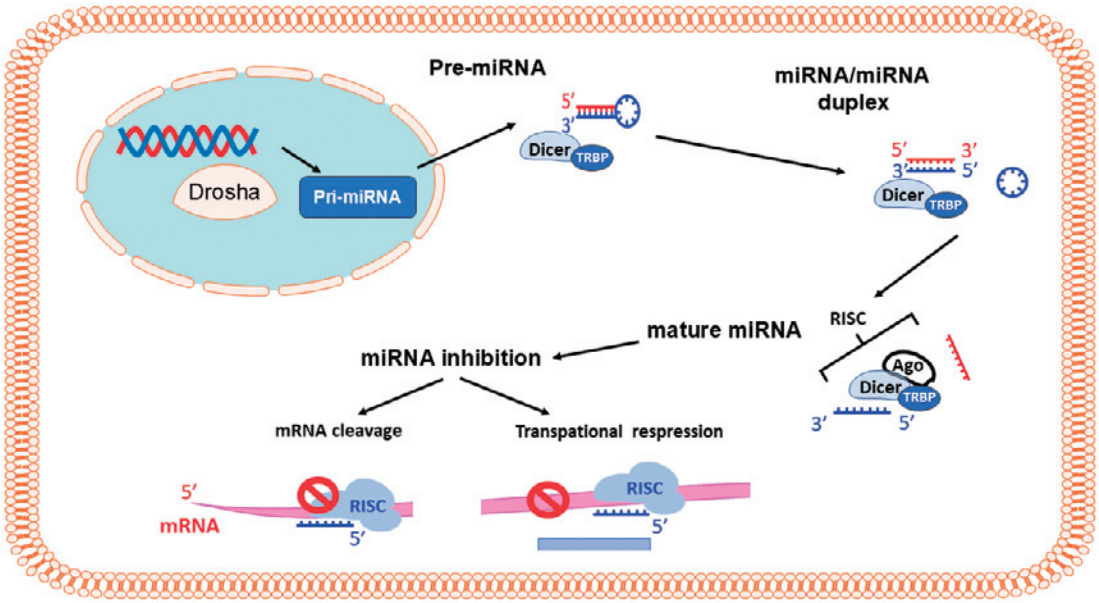

Fig. 1 microRNA maturation process
RISC: RNA-induced silencing complex

tion in the cell nucleus codes for proteins that are synthesized through transcription and translation to carry out cellular activities. Later, it was discovered that many RNAs, called noncoding RNAs (ncRNAs), do not code for proteins. ncRNAs were initially thought to be junk RNA, as they appeared to have no function. However, certain ncRNAs moderate mRNA translation and degradation by acting as a negative regulator that suppresses expression of target mRNA[8]. Because ncRNA regulates mRNA expression, it increases the complexity of gene expression, contributing to biological complexity and diversity. This becomes clear when examining the proportion of ncRNA among transcriptional products. In *E. coli*, about 20% of transcriptional products are ncRNAs, whereas in humans, it is estimated to be over 90%. Furthermore, ncRNAs are categorized by size: long noncoding RNAs comprise many bases, and microRNAs (miRNAs), a type of small RNA, consist of approximately 20 bases.

miRNAs are single-stranded, noncoding RNA molecules with 20-25 nucleotides. Triggered by stimuli such as anesthesia, precursor miRNA (pre-miRNA) is produced from nuclear DNA through Drosha cleavage. The pre-miRNA is then cleaved by the Dicer/transactivation response element RNA-binding protein complex, forming a miRNA/miRNA duplex, which subsequently matures into miRNA. The miRNA-induced silencing complex (miRISC) is formed when Ago1 to Ago4 proteins bind to the mature miRNA, with Ago2 being essential for the cleavage of the target mRNA. miRNAs also function as negative regulators by modulating mRNA translation and degradation, thereby suppressing expression of target mRNA, although the function of miRNA depends on its complementarity with the target mRNA. If the binding region is a perfect match, the mRNA is degraded. When complementarity is partial, miRNA inhibits translation[9]. In either case, miRNA remains a negative regulator of gene expression (**Fig. 1**). Humans have more than 1,500 miRNAs, but the roles of these miRNAs in normal and pathological cellular functions are unknown. The action of miRNA is complex, with a single miRNA targeting more than 100 mRNAs[10], and one mRNA being targeted by multiple miRNAs[11]. Thus, changes in a single miRNA can affect numerous pathways, leading to highly intricate effects. This complexity contributes to the biological diversity mentioned earlier. Changes in miRNA expression alter protein biosynthesis, leading to changes in cellular activity. In addition, miRNA can be transmitted to neighboring cells via gap junctions or secreted in extracellular vesicles, which are contained within the endoplasmic reticulum. These vesicles carry miRNA through the bloodstream to distant or other cells, thereby affecting protein biosynthesis in many different cells. Previous studies have demonstrated that miRNAs modulate various aspects of cell biology, including cell differentiation, proliferation, apoptosis, embryonic development, stress responses, stem cell renewal, and metabolism[12–16]. Therefore, miRNAs are important regulatory factors in

the onset and progression of perioperative diseases such as sepsis, ischemia-reperfusion injury, and cancer.

Research on miRNA can be broadly divided into three key areas. The first focuses on understanding the role of miRNA in disease development and progression. The second involves drug discovery aimed at targeting specific miRNAs responsible for those diseases. The third explores disease-specific miRNAs released into the bloodstream, which can serve as tumor markers or indicators of organ damage.

Gene Expression Changes Induced by Anesthetic Agents

A comprehensive study of gene changes induced by sevoflurane showed that the anesthetic affected expression of 1.5% of 10,000 genes. The gene expression patterns caused by sevoflurane differed by organ, suggesting that the effects of anesthetic agents vary across organs[17]. The representative gene expression changes caused by sevoflurane include suppression of mRNA related to circadian rhythms in the brain[18], changes in the expression of mRNA related to drug metabolism in the liver[19], and changes in the expression of mRNA regulating vascular tone in pulmonary circulation[20]. Protein expression directly affects organ function. A previous study used proteomics analysis to comprehensively examine anesthetic-induced changes in protein expression in multiple organs[21]. However, the results were inconsistent with gene expression changes reported earlier. The present author hypothesizes that the difference was attributable to miRNAs.

The present author investigated changes in miRNA expression induced by anesthetics in the brain[22], lungs[23], and liver[7]. Of the 177 miRNAs expressed in the rat liver, the expression of 46 miRNAs was altered by sevoflurane or propofol, and the differences were significant, particularly in miR-142-3p, miR-29a, and miR-378[7]. In rat lungs, sevoflurane significantly altered the expression of 20 miRNAs[23], whereas in the rat hippocampus, sevoflurane and propofol caused significant differences in 14 miRNAs[22]. These findings indicate that different drugs induce distinct changes in miRNA expression and that the patterns of miRNA expression vary by organ. Because miRNA does not have a one-to-one correspondence with its target mRNA and exhibits complex effects within and between cells, as well as remotely, drug- and organ-specific changes in mRNA expression caused by anesthetics likely involve complex alterations. In other words, the effects of anesthetics appear to be quite intricate.

Diseases and miRNA: Anesthesia and Perioperative Management

This section will discuss cardiovascular disease and cancer as areas related to perioperative management via miRNAs.

Cardiovascular Disease

An important miRNA involved in atherosclerosis is miR-155. It was discovered in plaques from carotid artery stenoses and targets the BCL6 protein, which is related to inflammatory activity. Overexpression of miR-155 suppresses BCL6, consequently enhancing the pro-inflammatory activity of macrophages and leading to atherosclerosis[24]. Heart failure is a significant complication after non-cardiac surgery, and evidence indicates that miR-208 contributes to cardiac remodeling and a reduction in cardiac function. Increased miR-208 expression is correlated with a greater decline in left ventricular contractility. In prognostic studies, elevated miR-208 levels were linked to worse survival outcomes[25]. MicroR-208 is both a predictive factor for heart failure and cardiac death and a potential therapeutic target. Research on aging and cardiovascular diseases has shown that miR-34 is an important gene. Studies using myocardial biopsy samples reported a correlation between age and the expression level of miR-34[26]. In addition, the introduction of miR-34 into mice resulted in impaired cardiac function, suggesting that it is a cause of age-related decline in cardiac function. MiR-34 targets PNUTS, which is involved in telomere maintenance and DNA damage, and inhibition of PNUTS by miR-34 is said to cause telomere shortening. Similar to miR-208, miR-34 is also being studied as a potential therapeutic target.

Cardiovascular Surgery

Cognitive impairment, a severe complication after open-heart surgery, affects both the short-term postoperative period and long-term survival and quality of life. Cerebral hypoperfusion, inflammatory responses, and microthrombosis are risk factors for cognitive impairment after cardiovascular surgery with cardiopulmonary bypass. miR-124-3p, which has neuroprotective effects due to its anti-inflammatory and anti-apoptotic properties, decreased, indicating a reduction in neuroprotective miRNA. This suggests that changes in miRNA expression caused by cardiopulmonary bypass could lead to postoperative cognitive impairment[27].

Cancer

The numerous studies of the effects of anesthetics on cancer cells can be broadly categorized into three types. The first category includes studies that evaluate the di-

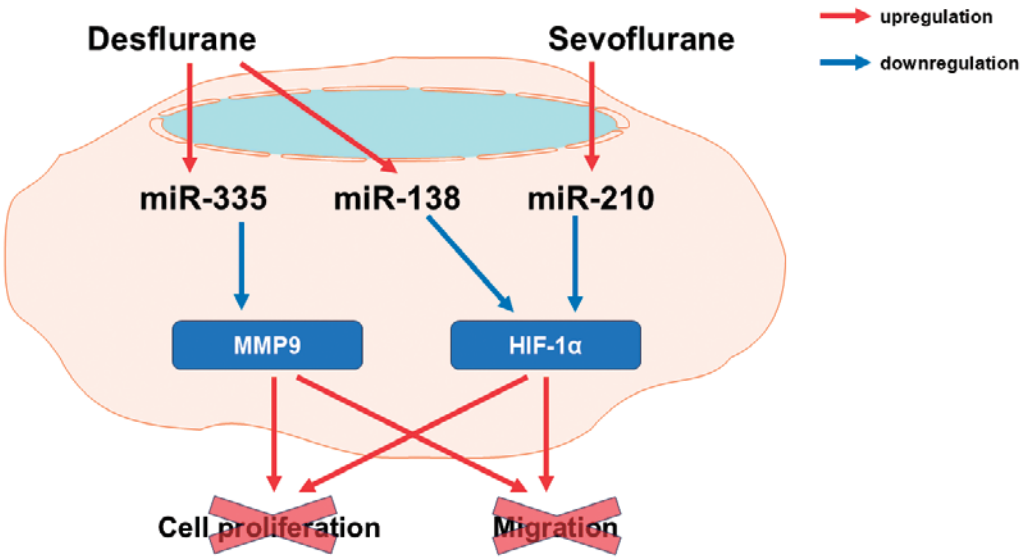

Fig. 2 Effects of anesthetic agents on glioma cells
Inhalational anesthetics attenuate glioma cell (H4) malignancy via upregulation of anticancer miRNA expressions. Sevoflurane exposure to H4 cells decreases H4 cell proliferation and migration via HIF-1α by miR-210 upregulation. Desflurane exposure to H4 cells decreases H4 cell proliferation and migration via HIF-1α and MMP9 by miR-138 and miR-335 upregulation, respectively.

rect effects on cancer cells, such as their migratory ability, invasiveness, and proliferation, the second category involves studies of intercellular communication, and the third focuses on immune function. Anesthetics can alter intercellular communication and immune function, either through the direct effect of the drugs themselves or by modifying mediators released by cancer cells.

First, the direct effects on cancer cells will be summarized. One study examined the effects of propofol on the migration and invasiveness of hepatocellular carcinoma cells[28]. In that study, 50 μg/mL of propofol inhibited migration and invasiveness by 90%, as compared with the control group. Furthermore, 10 μg/mL of propofol reduced the migration, invasiveness, and DNA synthesis of gastric cancer cells by 50%[29]. However, such high doses are not administered in clinical practice, and concentrations of 10-50 μg/mL near cancer cells are not typically achieved. When colorectal cancer cells were exposed to 2.5 vol% sevoflurane and 12 vol% desflurane for 3 or 6 hours, sevoflurane enhanced the activity of colorectal cancer cells, and desflurane suppressed it[30]. Many studies of anesthetics and cancer cells suggest that propofol has an inhibitory effect on cancer cells, whereas inhalational anesthetics tend to promote their activity. However, questions remain. Do anesthetics have a consistent trend of exacerbating or suppressing cancer cell activity, depending on the drug? Is it true that inhalational anesthetics worsen the activity of cancer cells? Are sevoflurane and desflurane similar in their effects? Further, does the effect remain the same across different types of cancer? To address these questions, the author investigated the effects of inhalational anesthetics on two types of cancer cells.

The present author investigated the effects and mechanisms of administering 3.6% sevoflurane and 10.3% desflurane for 2 hours on glioma and ovarian cancer. Sevoflurane and desflurane affect tumor cell activity by altering expressions of major key oncoproteins—hypoxia-inducible factor 1α (HIF-1α) and matrix metalloproteinase (MMP)—which are crucial for cancer progression[31,32]. These proteins are involved in cell proliferation[33,34], tissue remodeling, and cell migration[35] through degradation of extracellular matrix proteins. I hypothesized that these effects of sevoflurane and desflurane are mediated via miRNAs (miR-138, 210, 335) that regulate these proteins. Sevoflurane and desflurane both reduced the migratory and proliferative abilities of glioma cells; however, the mechanisms involving miRNA and protein expression differed. Sevoflurane inhibited cell activity through the miR-210/HIF-1α pathway, whereas desflurane exerted its inhibitory effects via the miR-138/HIF-1α and miR-335/MMP9 pathways[36](**Fig. 2**). In contrast, ovarian cancer cells showed increased motility and proliferation abilities when exposed to sevoflurane and desflurane. The mechanism showed that sevoflurane enhances cellular activity through the miR-138/HIF-1α and miR-210/HIF-1α pathways, whereas desflurane does so via the miR-138/

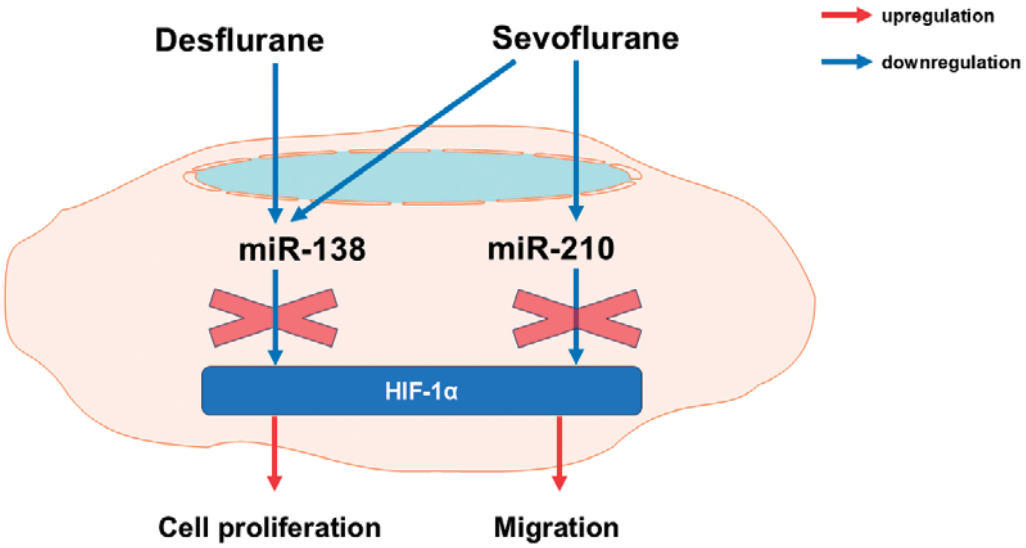

Fig. 3 Effects of anesthetic agents on ovarian cancer cells
Inhalational anesthetics enhance ovarian cancer cell (SKOV3) malignancy by downregulating anticancer miRNA expressions. Sevoflurane and desflurane exposure to SKOV3 cells increases SKOV3 cell proliferation and migration via HIF-1α by miR-138 downregulation. Only sevoflurane decreases miR-210 expression, leading to an enhancement of SKOV3 cell malignancy via HIF-1α.

HIF-1α pathway[37](**Fig. 3**). As mentioned above, the effects of inhalational anesthetics differ by organ. The evidence indicates that inhalational anesthetics may exacerbate or suppress cellular activity, depending on the type of cancer, and that the mechanisms of action differ in relation to the inhalational anesthetic.

The next topic is intercellular communication. Extracellular vesicles (EVs) released from cancer cells contain mRNA, miRNA, and mediators, which reach other cancer cells and immune cells, thus affecting their function. Clinical studies have reported that the impact of miRNAs contained in EVs is affected by anesthetics[38]. In a study of colorectal cancer patients who underwent surgery under general anesthesia using propofol or sevoflurane, the miRNA in EVs released into the blood postoperatively was measured. Although expression of 28 types of miRNAs increased in both groups, 20 types increased only in the propofol group. No common miRNAs showed decreased expression between the two groups, but 16 types of miRNAs decreased in the propofol group. Both groups exhibited enhanced expression of miRNAs related to cell death; however, expression of miRNAs associated with suppression of cell proliferation, motility, and methylation, as well as promotion of apoptosis, changed only in the propofol group. These findings suggest that propofol is more likely to contribute to suppression of cancer cells through intercellular communication.

Role of MicroRNA in Clinical Applications

The key point of miRNA as a therapeutic target is that it can regulate multiple pathways, which suggests potential for effective action in multiple diseases. Acute kidney injury is a significant perioperative complication, and it has been reported that even a slight increase in perioperative creatinine level is associated with a prolonged hospital stay and increased mortality. In cases of acute kidney injury, plasma miR-210 expression is elevated, and miR-210 expression level has been identified as an independent predictor of survival and 28-day survival in patients with acute kidney injury[39]. In other words, miR-210 may be a novel biomarker for the diagnosis and prognosis of acute kidney injury, and its inhibitors may have potential as a treatment. Further, miRNA might also be a therapeutic target for cancer. In vivo studies using antisense oligonucleotides to silence miR-21, which is involved in tumorigenesis, confirmed that apoptosis in cancer cells is promoted and that tumor volume is reduced through inhibition of cell proliferation[40]. SPC3649 is a miR-122 inhibitor and the first drug to reach phase II clinical trials. Targeting liver-specific miR-122 had anti-inflammatory and anti-tumor effects in hepatitis C virus infection. In addition, miR-34a, known for its anti-tumor properties, has been targeted by the miR-34a promoter MPX34. A phase I clinical trial that was conducted for patients with unresectable hepatocellular carcinoma and hematological malignancies confirmed its safety in 85 patients[41]. In addi-

tion, miR-34a is involved in the development of multiple cancers, including brain cancer[42], esophageal cancer[43], gastric cancer[44], lung cancer[45], breast cancer[46], prostate cancer[47], and ovarian cancer[48], raising expectations for its potential as an anti-cancer drug. As previously mentioned, miR-34a is also involved in age-related changes in cardiac muscle, making it a potential candidate for heart failure treatment. One challenge in miRNA drug development is drug delivery and monitoring. Whether using miRNA inhibitors or promoters, a safe and efficient delivery strategy to the target cells is required. In clinical trials, drugs are designed to form complexes with miRNA agents to ensure delivery to target cells. Furthermore, because these drugs exert their effects by regulating protein biosynthesis, their half-life depends on the half-life of the target protein. Therefore, miRNA drugs cannot be monitored by measuring their concentration in blood. In addition, because of the exceptionally high stability of these drugs, they may remain inside cells for several weeks to months, raising concerns about the potential for unexpected long-term side effects.

Conclusion

In cardiology and cancer, miRNA research has advanced, leading to the identification of disease markers and drug development. However, the role of miRNA in perioperative management remains unclear. In the future, it is expected that changes in miRNA expression will be considered when selecting and administering anesthetic drugs perioperatively.

Availability of data and material: Not applicable.

Acknowledgements: Not applicable.

Funding: Not applicable.

Conflict of Interest: None.

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(Received, September 29, 2024)
(Accepted, November 27, 2024)