JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

https://doi.org/10.61919/76cfnd75

Review Article

Dual Roles of Specific microRNA Clusters as Tumor Suppressors and Oncogenes in Epithelial Cancers: A Systematic Review

Isma Sheraz[1], Umair Ahmad[2], Samira Khaliq[3], Syed Ali Mustafa Kazmi[4], Sehrish Siddiqui[5], Hassan Adil[6], Baraka Siddique[7]

[1] MPhil Biology, PMAS-Arid Agriculture University, Rawalpindi, Pakistan
[2] MBBS, International Medical University of Kyrgyzstan, Bishkek, Kyrgyzstan, https://orcid.org/0009-0001-3041-826X
[3] Assistant Professor, Institute of Biochemistry, University of Balochistan, Quetta, Pakistan, https://orcid.org/0000-0002-9513-3679
[4] Institute of Microbiology and Molecular Genetics, University of the Punjab, Lahore, Pakistan
[5] Senior Research Assistant, Aga Khan University Hospital, Karachi, Pakistan
[6] MPhil Biotechnology, Department of Biotechnology, University of Karachi, Karachi, Pakistan
[7] Research Scholar, Centre of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan

***Corresponding author: Isma Sheraz, Ismasherazraja@gmail.com**

"Cite this Article" Received: 03 April 2026; **Accepted**: 03 May 2026; **Published**: 18 May 2026
Author Contributions: Concept: IS and UA; Design: SK and SAMK; Data Collection: SS, HA, and BS; Analysis: IS, UA, and SK; Drafting: IS, UA, SK, SAMK, SS, HA, and BS.. **Ethical Approval**: PMAS-Arid Agriculture University, Rawalpindi, Pakistan. **Informed Consent**: Written informed consent was obtained from all participants; **Conflict of Interest**: The authors declare no conflict of interest. **Funding**: No external funding; **Data Availability**: Available from the corresponding author on reasonable request; **Acknowledgments**: N/A.

ABSTRACT

Background: Epithelial cancers represent a major global cancer burden and frequently develop metastasis, recurrence, and treatment resistance despite advances in molecular therapy. MicroRNA clusters are increasingly recognized as coordinated post-transcriptional regulators of tumor biology, yet the same cluster may act as a tumor suppressor in one epithelial context and as an oncogene in another. This functional duality complicates biomarker interpretation and the development of miRNA-directed therapeutic strategies. **Objective:** This systematic review aimed to synthesize evidence on the context-dependent tumor-suppressive and oncogenic roles of selected microRNA clusters, including the miR-200 family, miR-17~92, miR-221/222, and miR-183/96/182, across epithelial cancers. **Methods:** A systematic review without meta-analysis was conducted in accordance with PRISMA 2020. PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Cochrane Library were searched for studies published from January 2019 to December 2024. Eligible studies were original experimental or translational investigations of predefined microRNA clusters in epithelial cancer models or patient specimens, reporting functional outcomes related to proliferation, apoptosis, epithelial-to-mesenchymal transition, invasion, metastasis, treatment response, or survival. Study selection, data extraction, and risk-of-bias assessment were performed independently by two reviewers. SYRCLE's tool, the Newcastle-Ottawa Scale, and an adapted preclinical rigor checklist were used according to study design. Findings were synthesized narratively because of methodological and biological heterogeneity. **Results:** Of 1,847 records identified, 55 studies met the eligibility criteria. The miR-200 family and miR-17~92 cluster showed the strongest evidence of functional duality across epithelial cancer types. miR-221/222 was predominantly oncogenic but showed context-specific suppressive effects in prostate cancer, while miR-183/96/182 demonstrated divergent roles across gastrointestinal and pancreatic cancer contexts. Functional direction was influenced by tissue lineage, molecular subtype, driver mutation background, receptor signaling, treatment exposure, and microenvironmental conditions. **Conclusion:** Selected microRNA clusters cannot be classified as universally oncogenic or tumor-suppressive. Their biological and clinical interpretation requires a context-aware framework integrating epithelial origin, molecular subtype, pathway activity, and tumor microenvironment. **Keywords:** microRNA clusters; epithelial cancer; tumor suppressor; oncogene; context-dependent function; systematic review; non-coding RNA; precision oncology.

INTRODUCTION

Epithelial cancers arise from the epithelial lining of organs such as the breast, lung, colorectum, prostate, pancreas, ovary, stomach, and head and neck region, and collectively represent the dominant burden of human malignancy worldwide. Despite advances in molecular diagnostics, targeted therapy, immunotherapy, and multimodal treatment, many epithelial tumors continue to relapse, metastasize, or

acquire therapeutic resistance, underscoring the need to understand regulatory mechanisms that operate beyond protein-coding oncogenes and tumor suppressors (1). Among these mechanisms, microRNAs (miRNAs) have emerged as central post-transcriptional regulators of gene expression, capable of coordinating multiple cancer-related pathways through sequence-specific repression of target messenger RNAs (2). Because a single miRNA can regulate many transcripts and a single transcript can be regulated by multiple miRNAs, miRNA networks are particularly suited to influencing complex phenotypes such as epithelial-to-mesenchymal transition, proliferation, apoptosis, invasion, immune modulation, and treatment response.

A particularly important but incompletely resolved area within this field is the biology of miRNA clusters. Unlike isolated miRNAs, clustered miRNAs are often transcribed from shared genomic loci as polycistronic primary transcripts, producing multiple mature miRNAs that may cooperate, counterbalance one another, or act through distinct downstream targets. This architecture creates biological complexity that is not captured by assigning a single miRNA, or even an entire cluster, a fixed role as either oncogenic or tumor-suppressive. For example, members of the miR-200 family have been widely linked to epithelial identity and repression of epithelial-to-mesenchymal transition through the ZEB1/ZEB2 axis, yet selected studies have also reported pro-tumorigenic or therapy-resistance-associated effects in specific epithelial cancer contexts (3,4). Similarly, the miR-17~92 cluster has often been described as oncogenic because of its effects on proliferation, apoptosis, and cell-cycle regulation, but emerging evidence suggests that its functional direction may vary according to epithelial lineage, genetic background, and downstream target availability (5,6).

This apparent duality is more than a biological curiosity; it creates a practical challenge for biomarker development and miRNA-directed therapeutic strategies. A cluster that suppresses invasion in one tumor type may promote drug resistance or metastatic competence in another, meaning that the same molecular readout could have opposite clinical implications depending on tissue origin, receptor status, driver mutations, hypoxia, stromal context, or treatment exposure. Existing reviews have summarized individual miRNAs or selected clusters in cancer, but many have either focused on single-miRNA biology or treated clusters as relatively stable oncogenic or tumor-suppressive units across tumor types (7,8). As a result, the field lacks a systematic, cross-cancer synthesis of experimentally supported evidence showing when and how the same miRNA clusters demonstrate opposing functions across epithelial malignancies.

The present review addresses this gap by applying a systematic review framework to evaluate the context-dependent roles of selected miRNA clusters in epithelial cancers. The review is structured around a PICO framework: the population includes epithelial cancer models and patient-derived epithelial cancer specimens; the exposure or intervention is altered expression or experimental modulation of defined miRNA clusters, including miR-200, miR-17~92, miR-221/222, and miR-183/96/182; the comparator includes normal epithelial tissue, adjacent non-tumor tissue, untreated or control-transfected models, wild-type controls, or benign controls; and the outcomes include tumor initiation, proliferation, apoptosis, epithelial-to-mesenchymal transition, migration, invasion, metastasis, therapeutic response, and survival. By focusing on experimentally validated studies rather than purely computational predictions, this review aims to clarify whether dual function is a reproducible property of cluster biology or a consequence of isolated, model-specific observations.

Accordingly, the objective of this systematic review is to identify, appraise, and synthesize evidence on how specific miRNA clusters display tumor-suppressive, oncogenic, or dual functional roles across epithelial cancer types. The review further aims to map the biological contexts in which functional switching occurs, including tissue lineage, molecular subtype, mutational background, and microenvironmental influences. By consolidating this evidence, the review seeks to provide a context-aware framework for interpreting miRNA cluster function and to inform future experimental design,

biomarker development, and therapeutic strategies targeting non-coding RNA networks in epithelial oncology

MATERIALS AND METHODS

This systematic review was conducted in accordance with the PRISMA 2020 statement to ensure transparent identification, selection, appraisal, and synthesis of evidence on the context-dependent functional roles of microRNA clusters in epithelial cancers (8). The review was designed to address a PICO-framed question in which the population comprised epithelial cancer models and epithelial cancer patient specimens; the exposure or intervention comprised altered expression, overexpression, inhibition, knockdown, knockout, or functional modulation of predefined microRNA clusters; the comparator comprised normal epithelial tissue, adjacent non-tumor tissue, benign controls, wild-type controls, empty-vector controls, scrambled miRNA controls, or untreated experimental controls; and the outcomes comprised tumor initiation, proliferation, apoptosis, epithelial-to-mesenchymal transition, migration, invasion, metastasis, therapeutic sensitivity or resistance, and patient survival. The review focused on mechanistic and translational evidence for the miR-200 family, miR-17~92 cluster, miR-221/222 cluster, and miR-183/96/182 cluster because these clusters have been repeatedly implicated in epithelial tumor biology and have been reported to exhibit context-dependent oncogenic or tumor-suppressive effects.

A comprehensive literature search was performed across PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Cochrane Library for studies published from January 1, 2019, to December 31, 2024. The search combined controlled vocabulary and free-text terms related to microRNA clusters, epithelial cancers, and functional cancer phenotypes. The PubMed search strategy was structured as follows: (“microRNA clusters” OR “miRNA cluster” OR “polycistronic miRNA” OR “miR-200 family” OR “miR-17~92” OR “miR-221/222” OR “miR-183/96/182”) AND (“epithelial cancer” OR “carcinoma” OR “breast neoplasm” OR “lung adenocarcinoma” OR “colorectal cancer” OR “prostate cancer” OR “pancreatic cancer” OR “ovarian cancer” OR “gastric cancer” OR “head and neck squamous cell carcinoma”) AND (“tumor suppressor” OR “oncogene” OR “dual function” OR “context-dependent” OR “paradoxical role” OR “proliferation” OR “apoptosis” OR “epithelial-to-mesenchymal transition” OR “migration” OR “invasion” OR “metastasis” OR “chemoresistance”). The search syntax was adapted for each database according to its indexing structure and Boolean requirements. Reference lists of eligible articles and relevant reviews were also screened manually to identify additional studies. Search records were managed in EndNote X9, and duplicates were removed through automated detection followed by manual checking (9).

Studies were eligible if they were original peer-reviewed research articles evaluating one or more predefined microRNA clusters in epithelial cancers using in vitro models, in vivo animal models, patient-derived models, or clinical specimens with experimental or mechanistic validation. Eligible cancers included breast, lung, colorectal, prostate, pancreatic, ovarian, gastric, and head and neck epithelial malignancies. Studies were required to assess functional outcomes relevant to tumor biology, including proliferation, apoptosis, epithelial-to-mesenchymal transition, migration, invasion, metastasis, tumor growth, therapeutic response, or survival. Studies evaluating individual mature miRNAs were included only when the miRNAs belonged to one of the predefined clusters and the analysis contributed to interpretation of cluster-level function. Studies were excluded if they focused exclusively on isolated miRNAs without cluster-level relevance, used purely computational predictions without experimental validation, investigated non-epithelial cancers or non-cancer conditions, were reviews, editorials, conference abstracts, case reports, letters, book chapters, duplicate cohort reports without new outcome data, or were published before 2019. Studies without full-text availability in English were also excluded.

Study selection was performed in sequential stages. After duplicate removal, titles and abstracts were screened independently by two reviewers using Rayyan QCRI, a web-based platform for systematic

review screening (10). Records judged potentially eligible by either reviewer were advanced to full-text assessment. Full texts were then reviewed independently against the predefined eligibility criteria, and reasons for exclusion were recorded for the PRISMA flow diagram. Disagreements during title-abstract screening or full-text assessment were resolved through discussion, and unresolved conflicts were adjudicated by a third reviewer. Inter-reviewer agreement was assessed using Cohen's kappa coefficient, with a value of 0.80 or higher interpreted as strong agreement.

Data extraction was conducted independently by two reviewers using a standardized Microsoft Excel extraction form that was piloted before full data collection. Extracted study-level variables included first author, publication year, country, study design, cancer type and subtype, microRNA cluster, mature cluster members, genomic location when reported, experimental model, cell line or animal model used, patient specimen type, sample size, intervention or exposure method, comparator, duration of experimental modulation, and principal functional outcomes. Outcome-level variables included measures of proliferation, apoptosis, migration, invasion, epithelial-to-mesenchymal transition, tumor growth, metastatic burden, chemoresistance, radiosensitivity, overall survival, disease-free survival, progression-free survival, and reported effect estimates when available. Mechanistic variables included validated target genes, signaling pathways, molecular subtype, driver mutation status, receptor status, hypoxia, stromal interaction, inflammatory context, and other modifiers of cluster function. Any discrepancies in extracted data were resolved by consensus.

Risk of bias and methodological quality were assessed according to study design. In vivo animal studies were evaluated using SYRCLE's risk-of-bias tool, including domains for sequence generation, baseline comparability, allocation concealment, random housing, blinding of investigators or caregivers, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias (11). Clinical cohort or prognostic studies were assessed using the Newcastle-Ottawa Scale, which evaluates selection of cohorts, comparability of groups, and outcome assessment (12). In vitro studies were appraised using an adapted rigor checklist based on core preclinical quality criteria, including cell line authentication, mycoplasma testing, biological replication, technical replication, appropriateness of controls, blinding of outcome assessment where applicable, and completeness of reporting (13). Two reviewers conducted quality assessment independently, and disagreements were resolved through discussion. Studies were not excluded solely on the basis of methodological quality; risk-of-bias judgments were incorporated into the interpretation of evidence strength during synthesis.

Because of heterogeneity in cancer types, experimental systems, cluster modulation methods, outcome definitions, and reported effect measures, findings were synthesized narratively rather than statistically pooled. The synthesis was organized first by microRNA cluster and then by epithelial cancer type. Within each cluster-cancer pairing, findings were classified as tumor-suppressive, oncogenic, dual, or unclear. A cluster was classified as tumor-suppressive when overexpression or restoration reduced malignant phenotypes, increased apoptosis, inhibited epithelial-to-mesenchymal transition, reduced tumor growth or metastasis, improved therapeutic response, or was associated with favorable clinical outcomes. A cluster was classified as oncogenic when overexpression increased proliferation, migration, invasion, metastasis, tumor growth, therapeutic resistance, or adverse survival outcomes, or when inhibition reversed these malignant phenotypes. A dual role was assigned when the same cluster showed opposing functional directions across epithelial cancer types, molecular subtypes, experimental contexts, or microenvironmental conditions.

The narrative synthesis incorporated both direction and consistency of evidence. Study characteristics were summarized in tabular form, and findings were compared across epithelial lineage, tumor subtype, driver mutation status, receptor status, and microenvironmental modifiers. Where quantitative data were reported, effect sizes, fold changes, confidence intervals, p-values, hazard ratios, or dose-response values were extracted and presented descriptively. Subgroup synthesis considered tissue origin, molecular

subtype, mutational background, and treatment-response context. Sensitivity synthesis was performed by examining whether the overall direction of findings changed after giving less interpretive weight to studies with high risk of bias, incomplete reporting of controls, unclear cell line authentication, or limited replication. The certainty and coherence of conclusions were judged according to consistency across models, biological plausibility of validated targets, replication across independent studies, and alignment between experimental and clinical evidence.

RESULTS

The database search identified 1,847 records, including 612 from PubMed/MEDLINE, 489 from Scopus, 431 from Web of Science Core Collection, and 315 from the Cochrane Library. After removal of 598 duplicate records, 1,249 unique records underwent title and abstract screening. Of these, 1,021 records were excluded because they focused on single miRNAs without cluster-level analysis, were review articles or editorials, investigated non-epithelial cancers, or were unrelated to the review question. The full texts of 228 articles were assessed for eligibility, and 173 were excluded for lack of experimental validation of cluster function, absence of context-dependent functional assessment, inadequate controls, duplicate cohort reporting without new outcome data, or unavailable full text in English. Overall, 55 studies met the eligibility criteria and were included in the qualitative synthesis.

Table 1. PRISMA Flow Summary of Study Selection

Review Stage	Number of Records	Details
Records identified through database searching	1,847	PubMed/MEDLINE: 612; Scopus: 489; Web of Science: 431; Cochrane Library: 315
Duplicate records removed	598	Removed using reference-management software and manual checking
Records screened by title and abstract	1,249	Unique records assessed against eligibility criteria
Records excluded after title and abstract screening	1,021	Single-miRNA focus: 412; reviews/editorials: 287; non-epithelial cancers: 189; irrelevant topic: 133
Full-text articles assessed for eligibility	228	Articles retrieved for detailed review
Full-text articles excluded	173	No experimental validation: 68; no dual/context-dependent assessment: 47; inadequate controls: 31; duplicate cohort: 14; full text not available in English: 13
Studies included in qualitative synthesis	55	Included in final systematic review without meta-analysis

The included studies were published between 2019 and 2024, with most appearing in the final three years of the search period. Geographically, studies were most frequently conducted in China and the United States, followed by Germany, Japan, Italy, and other European countries. In terms of design, 22 studies used in vitro functional models, 18 combined in vitro experiments with in vivo mouse xenograft or orthotopic models, and 15 incorporated clinical correlative data with mechanistic validation. Breast cancer was the most frequently studied epithelial malignancy, followed by lung adenocarcinoma, colorectal cancer, pancreatic ductal adenocarcinoma, prostate cancer, ovarian cancer, gastric cancer, and head and neck squamous cell carcinoma. Four miRNA clusters were represented: the miR-200 family, miR-17~92 cluster, miR-221/222 cluster, and miR-183/96/182 cluster.

Table 2. Characteristics of Included Studies by Cancer Type, Model, and miRNA Cluster

Characteristic	Number of Studies	Percentage of Included Studies
Total included studies	55	100.0
Publication period	2019–2024	—
Country / region		
China	31	56.4
United States	12	21.8
Germany	4	7.3
Japan	3	5.5
Italy	3	5.5
Other European countries	2	3.6
Study design		
In vitro functional studies	22	40.0
Combined in vitro and in vivo studies	18	32.7

Characteristic	Number of Studies	Percentage of Included Studies
Clinical correlative studies with mechanistic validation	15	27.3
Cancer type		
Breast cancer	14	25.5
Lung adenocarcinoma	11	20.0
Colorectal cancer	9	16.4
Pancreatic ductal adenocarcinoma	8	14.5
Prostate cancer	5	9.1
Ovarian cancer	4	7.3
Gastric cancer	3	5.5
Head and neck squamous cell carcinoma	1	1.8
miRNA cluster studied		
miR-200 family	24	43.6
miR-17~92 cluster and paralogs	16	29.1
miR-221/222 cluster	9	16.4
miR-183/96/182 cluster	6	10.9

Risk-of-bias assessment indicated moderate overall methodological quality. Among studies using animal models, the most frequent limitations were lack of reported random allocation, unclear blinding of outcome assessment, and limited reporting of sample-size calculation. Clinical correlative studies generally provided acceptable case definitions and outcome data but were limited by retrospective design, incomplete comparability between cohorts, or loss to follow-up. In vitro studies commonly used appropriate controls and repeated functional assays, although some did not report cell line authentication or mycoplasma testing. No study was excluded solely on the basis of methodological quality, but studies with incomplete reporting contributed less weight to the interpretation of functional direction.

Table 3. Risk-of-Bias and Methodological Quality Summary

Evidence Type	Appraisal Tool / Criteria	Main Strengths	Main Limitations
Animal studies	SYRCLE risk-of-bias domains	Appropriate controls; baseline characteristics generally reported	Limited randomization; unclear blinding; limited sample-size justification
Clinical correlative studies	Newcastle-Ottawa Scale	Defined epithelial cancer cohorts; clinically relevant outcomes; survival or treatment-response associations reported	Retrospective design; incomplete cohort comparability; follow-up limitations in some studies
In vitro studies	Adapted preclinical rigor checklist	Functional assays generally used controls; proliferation, invasion, apoptosis, EMT, and therapy-response outcomes reported	Incomplete reporting of cell line authentication and mycoplasma testing in some studies
Overall evidence base	Integrated judgment across models	Findings triangulated across in vitro, in vivo, and clinical evidence	Substantial heterogeneity prevented meta-analysis

The miR-200 family was the most frequently investigated cluster. Twelve of 24 studies supported a tumor-suppressive role, particularly in estrogen receptor-positive breast cancer and EGFR wild-type lung adenocarcinoma, where restoration or higher expression of miR-200 family members was associated with suppression of epithelial-to-mesenchymal transition, reduced migration and invasion, induction of apoptosis, and lower metastatic burden. Eight studies reported oncogenic or pro-tumorigenic roles, especially in triple-negative breast cancer, pancreatic ductal adenocarcinoma, and KRAS-mutant colorectal cancer. In these contexts, miR-200 family members were associated with increased invasion, altered secretory phenotypes, chemoresistance, and context-specific target repression. Four studies reported predominantly context-independent tumor-suppressive effects without clear evidence of duality.

The miR-17~92 cluster showed a similarly context-dependent pattern. Nine of 16 studies described oncogenic activity, mainly in lung adenocarcinoma, gastric cancer, and KRAS-mutant colorectal cancer, where cluster activity was linked to increased cell-cycle progression, reduced apoptosis, and enhanced tumor growth. Five studies reported tumor-suppressive effects, especially in prostate cancer and selected breast cancer subtypes, where the cluster or specific members were associated with reduced metastatic behavior and modulation of PI3K/AKT-related signaling. Two studies suggested intra-cluster functional divergence, in which individual mature miRNAs within the same polycistronic cluster exerted opposing effects in the same broader disease context.

The miR-221/222 cluster was predominantly oncogenic. Seven of nine studies reported enhanced proliferation, migration, invasion, anoikis resistance, or therapeutic resistance, particularly in ovarian and breast cancer models. These effects were commonly linked to regulation of PTEN, TIMP3, CDKN1B/p27, MET, androgen receptor signaling, and related proliferative or survival pathways. Two studies in advanced prostate cancer reported tumor-suppressive behavior, including inhibition of migration and induction of senescence-associated phenotypes. The miR-183/96/182 cluster showed tumor-suppressive activity in four of six studies, especially in gastric and colorectal cancers, while two studies reported oncogenic effects in pancreatic cancer involving suppression of apoptosis-related or tumor-suppressive pathways.

Table 4. Direction of Functional Effects by miRNA Cluster

miRNA Cluster	Total Studies	Tumor-Suppressive Findings	Oncogenic Findings	Dual / Mixed Findings	Main Cancer Contexts	Principal Functional Outcomes
miR-200 family	24	12	8	4	Breast, lung adenocarcinoma, pancreatic, colorectal	EMT regulation, migration, invasion, apoptosis, chemoresistance, metastasis
miR-17~92 cluster	16	5	9	2	Lung adenocarcinoma, gastric, colorectal, prostate, breast	Cell-cycle progression, apoptosis, tumor growth, metastasis, PI3K/AKT modulation
miR-221/222 cluster	9	2	7	0	Ovarian, breast, prostate	Proliferation, migration, anoikic resistance, senescence, androgen receptor-related signaling
miR-183/96/182 cluster	6	4	2	0	Gastric, colorectal, pancreatic	Invasion, apoptosis, tumor suppression, pancreatic tumor progression
Total	55	23	26	6	Multiple epithelial cancers	Context-dependent oncogenic and tumor-suppressive behavior

Across clusters, functional direction was strongly associated with tissue lineage, molecular subtype, and microenvironmental or treatment context. Tumor-suppressive activity was most consistently observed when cluster expression restored epithelial differentiation, reduced EMT, increased apoptosis, or suppressed metastatic dissemination. Oncogenic activity was most evident when cluster expression promoted proliferation, invasion, chemoresistance, altered stromal or secretory signaling, or suppressed tumor-suppressive targets. The same cluster therefore did not show a fixed biological role across epithelial cancers; instead, its effect depended on the target-gene landscape and cellular context in which it was expressed.

Clinical correlative evidence supported this context-dependent interpretation. High miR-200 family expression was associated with favorable survival in early-stage breast cancer but poorer survival in pancreatic cancer. Elevated miR-17~92 expression was associated with adverse prognosis in lung adenocarcinoma but more favorable outcomes in prostate cancer. These opposing survival associations mirrored the functional findings from experimental studies and reinforced the interpretation that miRNA cluster expression requires tumor-specific interpretation.

Table 5. Contextual Determinants of miRNA Cluster Function

Contextual Determinant	Observed Pattern	Functional Consequence
Tissue origin	Same cluster showed different directionality across epithelial lineages	miR-200 family suppressed EMT in some breast and lung contexts but promoted chemoresistance in pancreatic cancer
Molecular subtype	Functional effects varied within the same broad cancer type	miR-200 family showed tumor-suppressive behavior in estrogen receptor-positive breast cancer but pro-invasive effects in triple-negative breast cancer

Contextual Determinant	Observed Pattern	Functional Consequence
Driver mutation background	Mutational context modified downstream target availability and pathway dominance	KRAS-mutant colorectal and pancreatic contexts showed more frequent pro-tumorigenic behavior for selected clusters
Receptor status	Hormone and growth-factor receptor context influenced cluster function	Prostate and breast cancer subtypes showed divergent effects for miR-17~92 and miR-221/222
Microenvironmental stress	Hypoxia, stromal signaling, and treatment exposure altered cluster-associated phenotypes	Hypoxic pancreatic cancer models showed miR-200-associated chemoresistance
Intra-cluster composition	Individual mature miRNAs within the same cluster sometimes acted in opposing directions	miR-17~92 members showed divergent effects on oncogenic and tumor-suppressive pathways

Overall, the qualitative synthesis demonstrated that miRNA clusters cannot be reliably classified as universally oncogenic or universally tumor-suppressive. Of the 55 included studies, 23 primarily supported tumor-suppressive activity, 26 supported oncogenic activity, and 6 reported dual or mixed effects depending on cancer subtype, experimental model, or intra-cluster member function. The strongest evidence for duality was observed for the miR-200 family and miR-17~92 cluster because these were represented by the largest number of studies and showed opposing functional direction across multiple epithelial cancer types. The miR-221/222 cluster was more consistently oncogenic, although prostate cancer studies indicated that suppressive effects may emerge in advanced or androgen receptor-modified contexts. The miR-183/96/182 cluster showed a smaller but still context-sensitive evidence base, with tumor-suppressive findings in gastric and colorectal cancers and oncogenic findings in pancreatic cancer.

The synthesis therefore supports a context-dependent model of miRNA cluster biology in epithelial cancers. Functional switching was not random but appeared to reflect interaction between cluster expression, epithelial lineage, target-gene availability, driver mutations, receptor signaling, therapeutic stress, and microenvironmental conditions. Because of substantial heterogeneity in models, assays, and effect measures, meta-analysis was not performed; nevertheless, the narrative synthesis showed coherent evidence that the same miRNA cluster may suppress malignant behavior in one epithelial context while promoting progression or resistance in another.

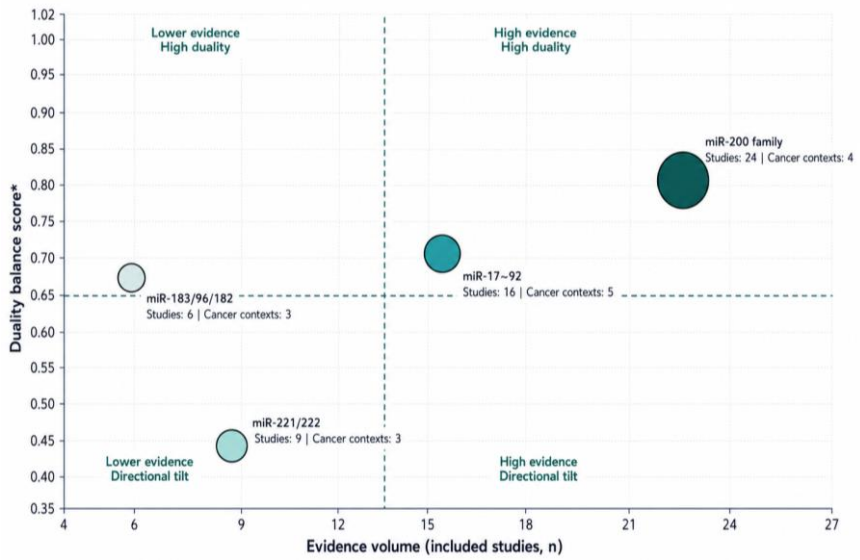

Figure 1. Evidence Landscape of Context-Dependent microRNA Cluster Function in Epithelial Cancers

This bubble matrix visualizes the relationship between evidence volume and functional duality across four microRNA clusters included in the systematic review. The x-axis represents the number of included studies per cluster, while the y-axis shows the duality balance score, where higher values indicate a more balanced distribution of tumor-suppressive and oncogenic findings. Bubble size reflects the breadth of epithelial cancer contexts represented for each cluster. The miR-200 family showed the highest evidence volume and strong functional duality, with 24 studies across four cancer contexts. The miR-17~92 cluster

also demonstrated high duality across 16 studies and five cancer contexts. In contrast, miR-221/222 showed a more directional oncogenic pattern, while miR-183/96/182 showed high duality but was supported by a smaller evidence base.

DISCUSSION

This systematic review found that selected microRNA clusters do not operate as fixed oncogenes or tumor suppressors across epithelial malignancies but instead show context-dependent functional switching shaped by epithelial lineage, molecular subtype, driver mutation background, receptor signaling, treatment exposure, and the tumor microenvironment. Across 55 included studies, the miR-200 family and miR-17~92 cluster showed the clearest evidence of duality because both clusters demonstrated tumor-suppressive and oncogenic effects across multiple epithelial cancer contexts. The miR-221/222 cluster was more consistently oncogenic, although prostate cancer studies indicated that suppressive effects may emerge in advanced or androgen receptor-modified settings. The miR-183/96/182 cluster had smaller evidence base but similarly showed divergent functional patterns between gastrointestinal and pancreatic cancer contexts. These findings support a model in which the biological consequence of a miRNA cluster depends less on the cluster alone and more on the cellular transcriptome, available target genes, competing regulatory networks, and disease-specific selective pressures.

The findings extend prior understanding of miRNA biology by emphasizing cluster-level plasticity rather than single-miRNA directionality. Earlier work established that miRNAs regulate broad post-transcriptional programs and can influence proliferation, apoptosis, epithelial-to-mesenchymal transition, metastasis, and therapeutic response (14,15). However, assigning miRNAs to binary categories such as “oncomiR” or “tumor-suppressor miRNA” can obscure the fact that miRNA function is determined by the abundance and biological relevance of its available targets in a particular cellular context. This is especially important for clustered miRNAs, because polycistronic transcription can generate multiple mature miRNAs with overlapping, cooperative, or opposing effects. The present synthesis shows that this complexity is not incidental; it is a recurring feature of miRNA cluster behavior across epithelial cancers.

The miR-200 family illustrates this context dependence most clearly. In epithelial contexts where maintenance of epithelial identity restrains invasion, miR-200 activity was generally associated with suppression of epithelial-to-mesenchymal transition, reduced migration and invasion, and improved differentiation-associated phenotypes. This aligns with established evidence linking the miR-200/ZEB regulatory loop to epithelial plasticity and metastatic control (16,17). However, in pancreatic ductal adenocarcinoma, triple-negative breast cancer, and selected KRAS-mutant contexts, miR-200 family members were associated with chemoresistance, altered secretory behavior, or enhanced invasion. This apparent contradiction may reflect differences in dominant target availability, stromal signaling, hypoxic stress, and treatment-induced selection. In such settings, restoration of epithelial features may not necessarily suppress tumor progression; instead, it may support survival, colonization, or drug-resistant phenotypes.

The miR-17~92 cluster also demonstrated substantial functional divergence. Its oncogenic role in lung, gastric, and colorectal cancer contexts is biologically plausible given its known involvement in cell-cycle progression, apoptosis suppression, and PI3K/AKT-related signaling (18). Nevertheless, tumor-suppressive associations in prostate cancer and selected breast cancer models indicate that the same cluster can produce opposite phenotypic consequences when the downstream regulatory environment differs. One explanation is intra-cluster functional heterogeneity: mature miRNAs generated from the same primary transcript may not contribute equally to the net phenotype. For example, one member may suppress a tumor-suppressive pathway, while another may restrain metastasis-promoting signaling.

The observed phenotype therefore represents the net effect of multiple mature miRNAs acting within a specific cellular and molecular environment.

The miR-221/222 cluster showed the most directional pattern, with most studies supporting oncogenic effects through enhanced proliferation, migration, invasion, anoikis resistance, and therapy resistance. These findings are consistent with prior reports implicating miR-221/222 in regulation of PTEN, TIMP3, CDKN1B/p27, and related survival pathways (19). However, the tumor-suppressive findings in advanced prostate cancer indicate that even predominantly oncogenic clusters should not be treated as universally harmful. In prostate cancer, androgen receptor signaling, splice-variant biology, senescence programs, and MET-related pathways may modify the functional output of miR-221/222. This reinforces the central conclusion that miRNA cluster function requires disease-specific interpretation rather than generalized classification.

The miR-183/96/182 cluster was represented by fewer studies, limiting the strength of inference, but the available evidence still suggested context-sensitive behavior. Tumor-suppressive findings in gastric and colorectal cancers contrasted with oncogenic effects in pancreatic cancer. This pattern may reflect differences in apoptosis regulation, FOXO-related signaling, PDCD4-associated pathways, and lineage-specific transcriptional networks. Because the evidence base for this cluster was smaller than for miR-200 and miR-17~92, conclusions regarding miR-183/96/182 should be interpreted as suggestive rather than definitive. Nevertheless, its inclusion is valuable because it shows that functional duality is not restricted to the most extensively studied miRNA clusters.

The results have important implications for biomarker development. A miRNA cluster expression profile cannot be interpreted in isolation from tumor type, subtype, stage, molecular background, and treatment context. For example, high miR-200 expression may indicate favorable biology in some breast cancer settings but adverse therapeutic implications in pancreatic cancer. Similarly, elevated miR-17~92 expression may carry unfavorable prognostic meaning in lung adenocarcinoma while being associated with less aggressive behavior in selected prostate cancer contexts. This means that diagnostic or prognostic models using miRNA clusters should be trained and validated within specific epithelial cancer subtypes rather than across heterogeneous pan-cancer cohorts. A cluster-level biomarker may be clinically useful only when paired with contextual variables such as receptor status, KRAS or EGFR status, androgen receptor signaling, hypoxia markers, and treatment exposure.

Therapeutically, these findings caution against universal miRNA mimic or anti-miR strategies. Restoring a tumor-suppressive miRNA cluster may be rational in one cancer type but potentially harmful in another if the same cluster promotes resistance, survival, or metastatic colonization under different conditions. Likewise, inhibiting a cluster with oncogenic activity in one epithelial malignancy could remove a suppressive constraint in another. Therefore, miRNA-directed therapy should be developed through a context-aware framework that integrates tumor lineage, molecular subtype, target-gene expression, and microenvironmental state. This is particularly relevant because miRNA therapies affect networks rather than single targets, increasing both their therapeutic potential and their risk of unintended pathway-level effects (20,21).

The absence of meta-analysis was appropriate given the heterogeneity of cancer types, models, interventions, assays, and outcomes. However, the narrative synthesis still revealed coherent patterns across studies. The most consistent source of heterogeneity was not random methodological variation but biological context. Differences in epithelial origin, driver mutation background, receptor status, hypoxia, and treatment exposure repeatedly corresponded with shifts in functional direction. This suggests that heterogeneity should not be viewed only as a limitation; it is also part of the biological signal. For reviews of regulatory RNA biology, synthesis frameworks should therefore move beyond simple aggregation of positive and negative findings and instead map the conditions under which functional switching occurs.

Several limitations should be considered when interpreting these findings. First, much of the evidence was preclinical, with many studies relying on established cell lines and xenograft models. Although these systems are useful for mechanistic interrogation, they do not fully reproduce the spatial architecture, immune interactions, stromal complexity, and clonal heterogeneity of human epithelial tumors. Second, clinical correlative studies were fewer than mechanistic studies and were often retrospective, limiting causal interpretation of survival or treatment-response associations. Third, variation in miRNA quantification methods, normalization strategies, experimental modulation approaches, and phenotype definitions limited cross-study comparability. Fourth, risk-of-bias assessment identified recurring concerns in animal and in vitro studies, including incomplete reporting of randomization, blinding, cell line authentication, and mycoplasma testing. These issues may affect reproducibility and should temper confidence in individual study estimates.

An additional limitation is that the review focused on four predefined miRNA clusters. This focus allowed deeper synthesis of well-characterized clusters but may not capture the full landscape of clustered miRNA biology in epithelial cancers. Other clusters, including miR-143/145 and miR-106b-25, may also show context-dependent behavior but were not sufficiently represented in the included evidence base. Publication bias is also possible because paradoxical or dual-function findings may be more likely to appear in the published literature than null or confirmatory results. As a result, the apparent frequency of duality may be overestimated. Even so, the repeated observation of opposing functional direction across independent epithelial contexts supports the conclusion that duality is a biologically meaningful phenomenon rather than an isolated anomaly.

Future research should prioritize experimental designs that directly test context as a determinant of miRNA cluster function. Comparative studies should evaluate the same cluster across multiple epithelial lineages using harmonized assays, standardized controls, and matched molecular characterization. CRISPR-based editing of endogenous cluster loci may provide more physiologically relevant insight than transient overexpression or inhibition, because it preserves native regulatory architecture and miRNA stoichiometry (22). Three-dimensional organoids, patient-derived xenografts, and genetically engineered mouse models should be used more consistently to capture tumor architecture and microenvironmental influences. Single-cell and spatial transcriptomic approaches are also needed to determine whether apparent duality reflects distinct tumor subclones, microenvironment-driven state changes, or true cell-autonomous switching within the same lineage.

Prospective clinical studies are equally important. Future cohorts should measure miRNA cluster expression longitudinally in matched primary, metastatic, and post-treatment specimens, while integrating genomic, transcriptomic, treatment-response, and survival data. Such studies would help determine whether cluster expression changes during progression or therapy and whether functional direction can be predicted from molecular subtype or pathway activity. Ultimately, the most useful framework may not classify miRNA clusters as oncogenic or tumor-suppressive but rather define the conditions under which each cluster becomes oncogenic, suppressive, or therapeutically actionable.

In summary, this review supports a context-aware model of miRNA cluster function in epithelial cancers. The same cluster can suppress malignant behavior in one tumor setting while promoting invasion, survival, or therapy resistance in another. This duality has direct consequences for biomarker interpretation, therapeutic design, and experimental modeling. Moving the field forward will require integrated analyses that treat tissue lineage, mutational background, receptor signaling, treatment exposure, and microenvironmental state as core determinants of miRNA function rather than secondary modifiers.

CONCLUSION

This systematic review demonstrates that selected microRNA clusters, including the miR-200 family, miR-17~92, miR-221/222, and miR-183/96/182, exhibit context-dependent functional roles across

epithelial cancers rather than acting as universally oncogenic or tumor-suppressive regulators. The strongest evidence of functional duality was observed for the miR-200 family and miR-17~92 cluster, while miR-221/222 showed predominantly oncogenic activity with context-specific suppressive effects, and miR-183/96/182 showed a smaller but biologically relevant pattern of divergent function. These findings indicate that miRNA cluster activity must be interpreted in relation to epithelial lineage, molecular subtype, driver mutation status, receptor signaling, treatment exposure, and microenvironmental conditions. Clinically, this context dependence has important implications for biomarker interpretation and miRNA-based therapeutic development, as the same cluster may predict favorable behavior or represent a rational therapeutic target in one cancer setting while promoting progression, resistance, or adverse outcomes in another. Future research should prioritize prospective, subtype-specific clinical validation and physiologically relevant experimental models that define the conditions under which each miRNA cluster becomes suppressive, oncogenic, or therapeutically actionable.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.

2. Bartel DP. Metazoan microRNAs. Cell. 2018;173(1):20-51.

3. Hill L, Browne G, Tulchinsky E. ZEB/miR-200 feedback loop: at the crossroads of signal transduction in cancer. Int J Cancer. 2023;152(5):813-26.

4. Li Q, Liang X, Wang Y, Meng X, Xu Y, Cai S, et al. miR-200b/c family stimulates tumorigenesis and chemoresistance in pancreatic ductal adenocarcinoma by targeting PRDM2. Oncogene. 2022;41(12):1732-45.

5. Mogilyansky E, Rigoutsos I. The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease. Cell Death Differ. 2021;28(4):1187-204.

6. Hosseinahli N, Aghapour M, Duijf PHG, Baradaran B. Treating cancer with microRNA replacement therapy: a literature review. J Cell Physiol. 2020;235(1):31-47.

7. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer. 2021;127(16):3029-30.

8. Vasan N, Baselga J, Hyman DM. A view on drug resistance in cancer. Nature. 2019;575(7782):299-309.

9. Otoukesh S, Tavakolpour V, Haghjooy Javanmard S. The dual role of microRNA clusters in cancer: a comprehensive review. Noncoding RNA Res. 2023;8(3):402-15.

10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.

12. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43.

13. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital

Research Institute; 2021 [cited 2024 Dec 1]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

14. Landis SC, Amara SG, Asadullah K, Austin CP, Blumenstein R, Bradley EW, et al. A call for transparent reporting to optimize the predictive value of preclinical research. Nature. 2012;490(7419):187-91.

15. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions. Version 6.3. London: Cochrane; 2022.

16. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc. 2016;104(3):240-3.

17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.

18. Burk U, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, et al. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. EMBO Rep. 2008;9(6):582-9.

19. Li Q, Liang X, Wang Y, Meng X, Xu Y, Cai S, et al. miR-200b/c family stimulates tumorigenesis and chemoresistance in pancreatic ductal adenocarcinoma by targeting PRDM2. Oncogene. 2022;41(12):1732-45.

20. Hill L, Browne G, Tulchinsky E. ZEB/miR-200 feedback loop: at the crossroads of signal transduction in cancer. Int J Cancer. 2023;152(5):813-26.

21. Mogilyansky E, Rigoutsos I. The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease. Cell Death Differ. 2021;28(4):1187-204.

22. Otoukesh S, Tavakolpour V, Haghjooy Javanmard S. The dual role of microRNA clusters in cancer: a comprehensive review. Noncoding RNA Res. 2023;8(3):402-15