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MICRORIBONUCLEIC ACIDS: FROM LOST IN TRANSLATION TO THE NEW CENTRAL DOGMA OF MAMMARY NEOPLASMS IN HUMANS AND DOGS

ABSTRACT

For a considerable period, microRNAs (miRNAs) were commonly regarded as mere intermediate products devoid of any function. In the past decade, the increasing number of publications on the involvement of miRNAs in oncogenesis and the progression of neoplasms has made them attractive targets, since the malfunction of miRNAs in cells can lead to the dysregulation of tumor suppressor genes and/or oncogenes. The study in question employs an integrative literature review methodology to investigate the role of microribonucleic acids (miRNAs) in the context of human breast neoplasms (HBNs) and canine mammary neoplasms (CMNs). The impetus for this research stems from the evolving understanding of miRNAs, which were previously regarded as intermediate products devoid of function. However, they are now recognized as significant players in oncogenesis. There are numerous similarities between epidemiological factors and histopathological aspects of human breast neoplasms (HBNs) and canine mammary neoplasms (CMNs). Computational analyses have also demonstrated miRNA similarity between HBNs and CMNs. These findings suggest that the dog may serve as a suitable model for studying HBNs. miRNA assessment can assist in the diagnosis of mammary neoplasms, as profiles reveal differential expression linked to early detection, prognosis, and treatment.

Keywords: tumor biomarker; carcinogenesis; diagnosis; epigenetics; prognosis.

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1 INTRODUCTION

Approximately 75% of genetic information undergoes transcription, with only 1.5 to 2% of transcripts becoming messenger ribonucleic acids (mRNAs). The majority of transcription involves non-coding RNAs (ncRNAs), including microRNAs (miRNAs), short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs) (Solé *et al.*, 2019).

In the context of neoplasms, miRNAs can act as either tumor suppressors or oncogenes (oncomiRs), with their roles being directly related to expression levels and activities (Zhou *et al.*, 2008). Consequently, individual miRNAs exhibit multifaceted functions during carcinogenesis. The study justifies the use of comparative miRNA analysis in human and canine neoplasms as a means of identifying potential biomarkers for the early detection and treatment of neoplasms.

2 METHODOLOGY

This study employs an integrative literature review, focusing on human breast neoplasms (HBNs) and canine mammary neoplasms (CMNs). A PubMed search was conducted using the descriptors "human breast neoplasms," "canine mammary neoplasms," and "microRNAs" to identify 19 articles published between May 2008 and December 2023.

3 RESULTS

MIRNAS IN HUMAN BREAST NEOPLASMS (HBNS)

HBNs represent the most prevalent malignant disease among women globally, with an estimated 2.3 million documented cases. Despite extensive research linking HBNs to mutations in genes such as BRCA1/2 and PIK3CA, alongside familial predispositions, a mere 5 to 10% of HBNs can be attributed to genetic anomalies, leaving the majority of cases etiologically unclear (Catalanotto; Cogoni; Zardo, 2016).

Approximately 130 miRNA signatures have been identified that exhibit clinical potential for the precise recognition of HBNs. It is noteworthy that miRNAs are correlated with distinct biopathological features of HBNs, including hormone receptor expressions, tumor staging, vascular invasions, and proliferation indices. It is becoming increasingly evident that miRNAs can be used as a prognostic biomarker, enabling the differentiation of grades based on sample levels. Furthermore, there is growing evidence suggesting that miRNAs may be useful as a therapeutic monitoring marker (Anwar *et al.*, 2019).

Nevertheless, the application of miRNAs in HBNs is constrained by the lack of dependable panels for prognostic, diagnostic, or early intervention purposes (Piva *et al.*, 2013).

MIRNAS IN CANINE MAMMARY NEOPLASMS (CMNS)

Although HBNs and CMNs share several epidemiological and histopathological parallels, there is ongoing debate regarding the translatability of CMNs as a reliable HBN model (Cassali *et al.*, 2020). Computational analyses have identified sequence similarities, with 300 miRNAs in canines exhibiting a high degree of homology to their human counterparts (Zhou *et al.*, 2008). Nevertheless, a paucity of studies has evaluated miRNA expression levels in CMNs, particularly in serum or plasma (Table 1).

Pioneering research by Boggs *et al.* (2008) delved into miRNA expression profiles in CMNs, juxtaposing malignant mammary tumors against normal canine mammary tissues. This study demonstrated notable dysregulations and mirroring patterns observed in HBNs. In furtherance of this discourse, Von Deetzen *et al.* (2014) compared the expression of 16 microRNAs across diverse canine mammary tumor types, identifying distinct expression profiles.

Bulkowska *et al.* (2017) evaluate a miRNA expression profiling in CMNs, revealing overlaps with dysregulated miRNAs in HBNs. Recent in vitro investigations have highlighted exosomal miRNA patterns in CMNs, suggesting potential regulatory roles in vital oncogenic pathways, including HBNs. These findings offer the potential for discrimination between neoplastic and healthy states (Fish *et al.*, 2020).

4 CONCLUSIONS

The evaluation of miRNAs has the potential to be a valuable tool for the diagnosis of mammary neoplasms, with the ability to be measured in both blood and tissues. Profiling enables the identification of di-

▶ Table 1 - Summary of main studies on canine mammary neoplasms (CMNs) in relation to miRNA expressions and its characteristics

miRNA	let-7f	miR-210	miR-29b	miRs-21	miR-101	miR-125a	miR-125b	**miR-143**	**miR-145**	**miR-15a**	**miR-155**
Samples utilized	T; P	T; P	T; P; S	T; P; S	T; P	T; P; S	T; P	T; P	T; P	T; P	T
Methodology	TaqMan	SYBR	TaqMan; SYBR	TaqMan; SYBR	SYBR	SYBR	TaqMan; SYBR	SYBR	SYBR	TaqMan; SYBR	TaqMan; SYBR
Function	oncomiRs	oncomiRs	oncomiRs	oncomiRs	Suppressor	Suppressor	Suppressor	Suppressor	Suppressor	Suppressor	oncomiRs/ Suppressor
References	Boggs *et al.*, 2008; Bulkowska *et al.*, 2017	Von Deetzen *et al.*, 2014; Bulkowska *et al.*, 2017	Boggs *et al.*, 2008; Von Deetzen *et al.*, 2014; Bulkowska *et al.*, 2017; Jain *et al.*, 2021	Boggs *et al.*, 2008; LutfuL *et al.*, 2015; BulkowskA *et al.*, 2017; Jain *et al.*, 2021; Ramadan *et al.*, 2021	Von Deetzen *et al.*, 2014; Bulkowska *et al.*, 2017	Von Deetzen *et al.*, 2014; Bulkowska *et al.*, 2017	Boggs *et al.*, 2008; Bulkowska *et al.*, 2017	Von Deetzen *et al.*, 2014; Lutful *et al.*, 2015; Bulkowska *et al.*, 2017	Von Deetzen *et al.*, 2014; Lutful *et al.*, 2015; Bulkowska *et al.*, 2017	Boggs *et al.*, 2008; Bulkowska *et al.*, 2017	Boggs *et al.*, 2008; Lutful *et al.*, 2015

Note: T: tissue; P: plasma; S: serum; TaqMan: TaqMan qRT-PCR; SYBR: SYBR Green qRT-PCR; oncomiRs: Oncogene.
Source: survey data.

fferentially expressed miRNAs based on tumor characteristics, thereby facilitating early diagnosis, prognosis, and treatment. Nevertheless, the reliance on a single biomarker may prove to be inadequate. A more comprehensive understanding of the molecular mechanisms of miRNAs in HBNs is driving the development of diagnostic profiles, paving the way for miRNA-based personalized medicine. The observed similarities in miRNA expression patterns in dogs suggest the potential for canine models in future studies.

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