ONCOLOGY

Exploring the contrasts: in-depth analysis of human and canine mammary tumors - discoveries at the frontier

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Abstract

We have examined genomic and transcriptomic abnormalities in human and canine samples to evaluate the canine model's validity for breast cancer research, emphasizing similarities and differences. Both species commonly utilize serum tumor markers and noncoding microRNAs. Immunohistochemistry and immunocytochemistry were employed to illustrate and compare results based on histological diagnoses. In addition to these factors, similarities exist in spontaneous tumor occurrence, age of onset, hormonal influences, and disease progression, including tumor size, clinical stage, and lymph node involvement. Molecular traits such as hormone receptor status, Epidermal Growth Factor Receptor (EGFR), and proliferation markers (Ki67) further endorse the canine model's utility in breast cancer studies. The advancement of technologies facilitates the identification of new cancer-associated molecules, both coding and non-coding genes, underscoring their potential as prognostic/diagnostic biomarkers and therapeutic targets.

Keywords: human breast cancer (HBC), canine breast cancer (CBC), immune system, immunotherapy, comparative oncology, translational research

Introduction

Cancer has become the leading cause of death worldwide, under the pressure of an accelerated harmful environment, aged population, and socioeconomic risk factors [1]. According to GLOBOCAN 2020, breast cancer is classified as the leading pathology in terms of incidence and mortality in the female segment and the second cause of death within the overall oncological sector: approximately 9.2 million new cases in 2020, representing 11.7% of all malignant sites combined, and 684,996 further deaths in the same year, summing 6.9% of overall cancer-related death statistic [2].

In the last decades, animal models, especially the canine model has become an important translational model for human breast cancer [3,4]. The canine model represents an important translational factor, as dogs have become members of human families, sharing the same environment, exposure to the same risk factors and pathological stimuli (infectious agents, carcinogenic conditions and others) as their owners. The canine model is considered an exemplary model for the study of human breast cancer, due to the multiple similarities such as tumor spontaneity, intact immune environment, age of onset, influence of the hormonal profile on tumor development, disease evolution, clinical parameters (tumor size, clinical staging and invasion lymph node), tumor metastasis, as well as numerous molecular markers and genetic risk factors [4–7]. Another aspect that supports the use of the canine model as translational model is the fact that it spontaneously develops many types of tumors (lymphoma, leukemia, osteosarcoma, mammary tumors) [3,5,8]. Due to the common characteristics of the two models, the canine model represents an important model for the study of human

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breast cancer as well as for comparative studies that provide information about the prognosis and treatment of breast cancer [4,9].

Comparative oncology allows the therapeutic investigations of naturally occurring malignancies in terms of pathogenesis and therapy. Although several animal species, including the cat, horse and ferret, acquire malignancies that are of comparative interest with the human pathology, the dog has received the bulk of scientific and clinical attention thus far [10]. This is owing to the anatomic and physiologic similarities between dogs and human patients, their lengthy usage as a toxicological model in drug research, and, most significantly, the large number of dogs diagnosed and treated for cancer each year [11].

The present article summarizes the data found on PubMed on the use of canine animal models for breast cancer research, focusing on the immune molecular profile of breast tumors and its role in designing new immune-related therapeutic approaches.

Comparative oncology for human and canine breast cancer research

The canine animal model is an excellent example of comparative oncology because this species develops numerous tumors that have similar clinical and pathological features or incidence rates to specific human cancer [12,13]. In the case of both species, carcinogenesis is based on similar risk factors, represented by environmental toxins, obesity and advancing age. Canine mammary tumors are the most common cancers diagnosed in canine patients, representing 50% of all diagnosed neoplasias [14]. Annually, about 198 cases out of a total of 100,000 animals are reported [15]. It was observed that an essential aspect is that females sterilized after the second season did not have a protective effect on the risk of developing malignant breast tumors [14].

The canine model uniquely exhibits spontaneous breast gland neoplasms, with an incidence three times higher than humans [16]. Studies indicate breed influences on the occurrence of canine mammary tumors (CMT), with pure breeds showing an 80% frequency compared to 20% in mixed breeds. CMT is more prevalent in miniature or "toy" breeds, followed by medium and large breeds like German Shepherds and Labradors. Age also plays a vital role, with the highest prevalence in adult females aged 8-12 years [17]. Similar to humans, canine breast tumors show significant formations and metastases in adjacent lymph nodes or distant organs, correlating with unfavorable prognoses [18].

Hormonal dependence is crucial in both human and canine breast carcinomas, highlighting the significance of studying canine breast cancer under the one health-one medicine principle. Hormone and growth factor receptors, including PR, ERα, and HER2, play pivotal roles in breast cancer development and progression in both species. ER expression closely correlates with pathological aspects and tumor differentiation in canine mammary tumors (CMT) and human breast cancer (HBC), while PR expression is a key indicator of breast cancer recurrence. Additionally, PRLR, IGF1, and GH receptors contribute to breast carcinogenesis in both humans and dogs. These parallels underscore the relevance of comparative oncology in understanding and treating breast cancer across species [19,20]. The most important similarities between canine mammary tumors and human breast cancer are presented in table I.

In clinical practice, molecular classification plays a significant role, providing helpful information regarding prognosis, relapse risk, and the possibility of complete biological response. Thus, molecularly, breast cancers are classified as follows: luminal A (ER+, PR+, HER2-, KI67-), luminal B (ER+, PR+, HER2+/-, KI67+), HER2 over-expression (ER-, PR-, HER2+), basal-like (ER-, PR-, HER2-, CK5/6+) and normal-like tumors (ER+, PR+, HER2-, KI67, imitating the normal breast epithelium) [26,27].

Abadie et al. (2018), based on a canine breast cancer cohort, classified canine breast cancers from a molecular point of view as follows: luminal A, luminal B, no HER2-overexpressing and triple-negative either of the basal-like type (ER- and PR-, HER-2 and CK5/6+) or the non-basal-like type (ER- and PR-, EGFR, and CK5/6-) [28].

Table I. Similarities between canine mammary tumor and human breast cancer:

Similarity features	Humans	Dogs	References
Appearance	Spontaneous		
Age	Median age (62 years)	Median age (~10 years) equivalent to a 65.5 year old woman	[13,18]
Cycle of the disease	Identical		[13]
Dimensions of tumor	Similar		
Clinical stages	Identical		
Metastasis to lymph nodes	Identical		
Estrogen dependency	Long exposure to estrogen	Non-spayed females have a higher risk of developing breast tumors compared to females who were sterilized before age of 2 years	[21]
Molecular markers	In the carcinogenesis of breast tumors, a critical role is played by the multitude of identified genes.	The same genes play an identical role in canine tumor carcinogenesis.	[22–24]
Mammographic anomaly	Human and dogs' mammary neoplasm have similar microcalcifications and macrocalcifications		[23,25]

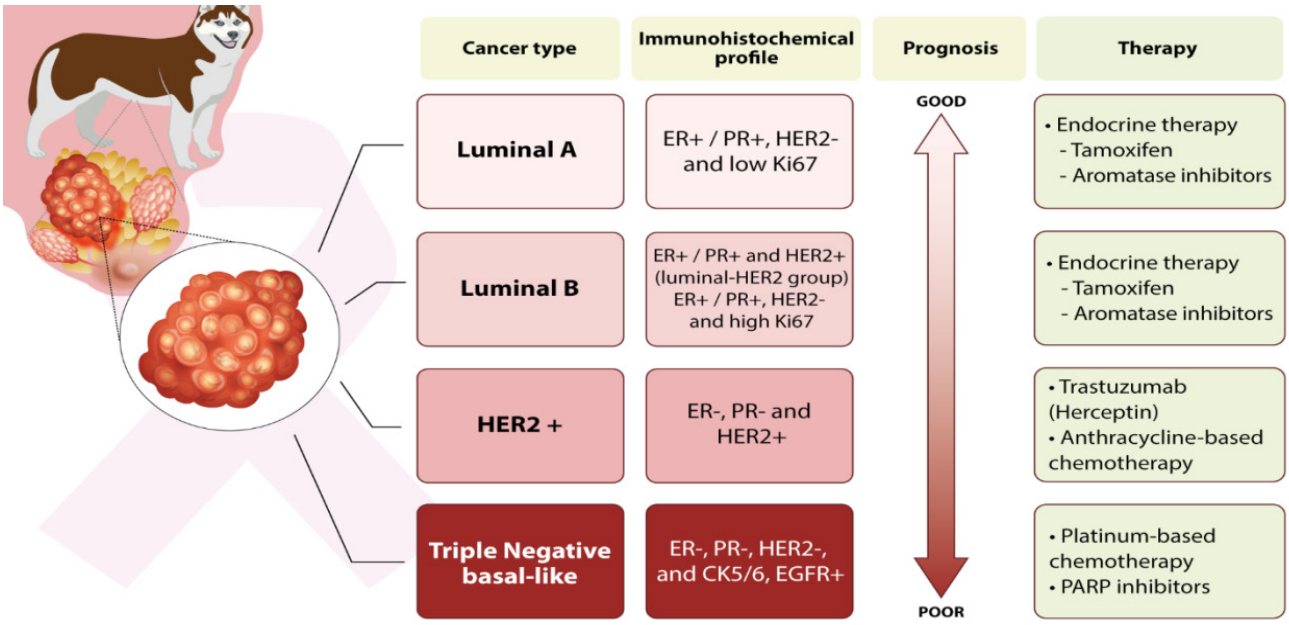

Figure 1. Therapeutic similarities for HBC and CMT: molecular subtype, histological grade, and prognosis.

Therefore, the canine animal model represents the model that spontaneously develops different forms of cancer, being an exemplary model for triple-negative breast cancer found in humans, as illustrated in figure 1.

Genetic makeup of human and canine breast cancer

DNA damage and genetic mutations are primary drivers of breast cancer development. However, replicating these characteristics in rodent models or cancer cell lines proves challenging due to their complexity. Factors such as prolonged hormone exposure or inherited defects in DNA, including those in tumor suppressor genes like BRCA1 and BRCA2, contribute to DNA damage and subsequent cancer development [29].

In addition to BRCA genes, several other genetic mutations contribute to breast cancer development, albeit in fewer cases and with a reduced risk compared to BRCA genes. Genes such as ATM, TP53, CHEK2, PTEN, CDH1, STK11 and PALB2 are implicated in familial breast cancer. Approximately 30 genes are known to play a role in breast cancer development, with about 5-10% of cases having a hereditary component. In animal models, particularly in the canine model, the risk of developing breast tumors mirrors that of humans, with hereditary factors playing a crucial role in tumor initiation and progression [30,31].

In canine mammary tumors (CMT), gene sequences for BRCA1 and BRCA2 proteins have been identified, with mutations associated with a four-fold increase in tumor risk. Additionally, protein interactions between BRCA2 and RAD51, involved in DNA repair, influence tumor development. Decreased BRCA1 expression correlates with malignancy, coinciding with increased Ki-67 and ERα negative markers [32,33].

KRAS mutations are more prevalent in CMT, while NF1 and SF3B1 mutations are observed in both CMT and HBC. MKI67 mutations hold oncological potential in CMT. However, certain genes like TP53, EGFR, ERBB2, ATM and CHEK2 show lower mutation frequencies in CMT compared to HBC. These findings underscore genetic parallels and differences between canine and human breast tumors, providing valuable insights into tumor biology and potential therapeutic targets [34].

Biomarkers of TNBC and CMTs: current biomarkers and potential future biomarkers

1. Current biomarkers (Biomarkers of cancer cell proliferation and apoptosis, Biomarkers of metastatic potential of the tumor, Biomarkers of angiogenesis, Biomarkers of inflammation)

1.1. Biomarkers of cancer cell proliferation and apoptosis (Ki-67, PCNA, p53)

Ki-67 and PCNA are primary proliferation biomarkers, while p53 signifies neoplastic transformation and apoptosis. Ki-67, a nuclear non-histone protein, peaks during mitosis, aiding in CMT diagnosis via IHC and cytology. High Ki-67 levels in human tumors indicate poor prognosis, yet predict chemotherapy response. Ki-67

evaluation, along with ER, PR, and HER-2, defines breast tumor subtypes [35].

Ki-67's serum biomarker potential, largely unexplored, correlates with tumor grade in dogs. In benign tumors, Ki-67 expression is low, contrasting malignant tumors linked to metastasis and poorer prognosis. Additionally, lymph node Ki-67 expression aligns with tumor tissue, suggesting its utility in prognosis assessment [36,37].

PCNA, a DNA polymerase protein, signifies the proliferation index (PI), peaking in late G1 phase and remaining elevated through G2 and M phases [38]. In human medicine, PCNA serves as a primary proliferation biomarker, often evaluated alongside other HBC markers [35]. In veterinary medicine, PCNA detection via IHC correlates with tumor characteristics like differentiation degree, mitotic index, and lymph node metastasis. Similar to Ki-67, PCNA expression is higher in malignant tumors, indicating poor prognosis and lower survival rates [39]. Combining PCNA with other biomarkers, particularly Ki-67, enhances prognostic accuracy due to its cell cycle-specific expression [38].

The p53 protein serves as a crucial biomarker in neoplastic transformation, cell division, and apoptosis regulation, acting as a tumor suppressor [40]. Mutated p53 leads to increased expression of p21, a cyclin-dependent kinase family member. In HBC, elevated p53 levels are associated with aggressive cancer types like TNBC and signify a poor prognosis and reduced survival time [41]. Overexpression of p53, predominantly evaluated via IHC, is linked to unfavorable outcomes in both human and veterinary contexts.

1.2. Biomarkers of metastatic potential of the tumor (E-cadherin, CEA, CA 15-3)

Cadherins are calcium-dependent transmembrane glycoproteins crucial for cell adhesion, maintaining tissue structure. E-cadherin, predominant in epithelial cells, plays a vital role in adhesion. Reduced E-cadherin expression correlates with tumor grade, lymph node involvement, tumor progression, aggressive metastasis, and poor prognosis in both human and veterinary contexts. Evaluation of E-cadherin alongside biomarkers like Ki-67 aids in assessing breast tissue characteristics. Additionally, other cadherin types like P-cadherin and N-cadherin contribute to cell adhesion processes [42].

Carcinoembryonic Antigen (CEA) is a protein expressed in small quantities by the gastrointestinal mucosa, found on epithelial cell membranes. Its overexpression is common in colon, breast, and lung cancer. In breast cancer (HBC), CEA serves as the primary serum biomarker, detected using various methods like radioimmunology (RIA) or electrochemical immunoassay with luminescence (ECL) [43]. Changes in CEA levels correlate with the therapeutic response in metastatic breast cancer, aiding in early detection of recurrence and metastasis [44,45]. Combining CEA with Cancer Antigen 15-3 (CA 15-3) enhances sensitivity and specificity in breast cancer diagnosis. Veterinary medicine observes elevated CEA levels in dogs with mammary gland tumors compared to healthy dogs [46]. However, CEA's diagnostic value in mammary tumors is optimized when evaluated alongside CA 15-3 due to its higher sensitivity. Despite CA 15-3's common usage, it lacks sensitivity in primary breast cancer diagnosis, primarily utilized for subsequent monitoring [43].

1.3. Biomarkers of angiogenesis

Neoplastic processes trigger the formation of new blood vessels, crucial for tumor nutrition and tissue homeostasis [47]. Malignant canine mammary tumors (CMTs) exhibit a higher density of neovessels compared to benign tumors [48]. Key biomarkers of angiogenesis include vascular endothelial growth factor (VEGF), its receptor (VEGFR), and von Willebrand factor VIII or CD31 [49].

VEGF, widely used in human medicine, stimulates angiogenesis and lymphangiogenesis at the tumor site. In both human breast cancer (HBC) and CMTs, elevated serum VEGF levels correlate with poor prognosis and low survival rates, particularly in aggressive, infiltrative tumors. VEGF serves as a biomarker for early tumor diagnosis, with increased sensitivity when correlated with CA 15-3 values [50,51].

1.4. Biomarkers of inflammation (COX, cancer associated stroma)

The cyclooxygenase enzyme (COX) plays a pivotal role in prostaglandin biosynthesis and tumor development. Cyclooxygenase 1 (COX-1) is expressed in normal tissues, while cyclooxygenase 2 (COX-2) is upregulated in inflammatory reactions and advanced tumors [52]. In both human breast cancer (HBC) and canine mammary tumors (CMT), high COX-2 levels are associated with malignancy, suggesting COX-2 inhibitors like meloxicam or piroxicam as potential treatments [52]. COX-2 inhibitors have shown promising results, particularly in inflammatory mammary carcinoma. COX-2 expression assessment is crucial for effective treatment with COX-2 inhibitors in both HBC and CMT [53].

Additionally, COX-2 expression promotes breast tumorigenesis and survival through various mechanisms, including the production of prostaglandin E2 (PGE2), which influences immune responses and tumor progression in HBC [54,55]. In CMT, COX-2 expression correlates with tumor aggressiveness, unfavorable prognosis, and metastasis, similar to HBC [56].

Cancer-associated stroma (CAS) markers like alpha-smooth muscle actin (αSMA) in both human and canine models indicate the role of cancer-associated fibroblasts (CAFs) in tumor development and progression. Common biomarkers between canine and human breast carcinoma, such as COL1A1, ACTA2, FAP, Caveolin-1,

FGF2, COL11A1, COL8A2, and ADAM12, highlight shared pathways in breast cancer pathogenesis [57]. These findings underscore the value of comparative oncology in understanding breast cancer biology and developing novel therapeutic strategies.

2. Potential future biomarkers – miRNAs (ncRNAs) and exosomes

2.1. Non-exosomal miRNAs

MicroRNAs (miRNAs) serve as promising non-invasive biomarkers for breast cancer (BC) and canine mammary tumors (CMT), influencing key tumoral processes like proliferation, invasion, and metastasis [58,59].

In CMT, 502 precursors and 453 mature miRNAs were identified, resembling patterns observed in HBC. Studies revealed altered expression levels of representative miRNAs between HBC and CMT, with miR-145 showing a unique pattern in humans. While miRNAs like miR-21 and miR-29b are upregulated in CMT, miR-15a and miR-16 exhibit a decrease [60].

Certain miRNAs, including miR-141 and miR-143, play roles in regulating tumor suppressor genes [61]. Although miRNAs mainly influence tumor metastasis, they aren't specific markers for metastasis. Validation studies identified several miRNAs associated with non-metastatic CMT, shedding light on their role in tumorigenesis [62].

2.2. miRNA-21

Overexpression of miR-21 is a common indicator of pathological growth or cellular stress and is among the most abundant miRNAs expressed in mammals. Physiologically, miR-21 regulates cell growth, migration, and invasion, while in carcinogenesis, it acts as an oncomiR by inhibiting tumor cell apoptosis [63,64].

Elevated miR-21 expression distinguishes clinically healthy bitches from those with mammary tumors, playing a role in metastasis and serving as a proposed biomarker [65,66]. In breast cancer, increased miR-21 expression correlates with enhanced cell proliferation, migration, invasion, metastasis, angiogenesis, and advanced tumor stage, with a poorer prognosis [67,68].

Inhibition of miR-21 expression suppresses tumor growth and metastasis, making it a sensitive non-invasive biomarker for cancer screening, progression, and detection in both human breast cancer and canine mammary tumors [69].

2.3. miR-29b

Another non-invasive biomarker with diagnostic and prognostic potential in breast cancer and canine mammary tumors is miR-29b, part of the miR-29 family. Alongside miR-29a and miR-29c, it regulates tumor cell processes like proliferation, apoptosis, metastasis, fibrosis, and angiogenesis, acting as both an oncomiR and tumor suppressor [70,71].

In canine mammary tumors, miR-29b expression was observed, with the canine SNP cell line showing significantly higher expression compared to serum samples from dogs with mammary tumors [60,65]. Similarly, in breast cancer, miR-29b is overexpressed in tumor cells, influencing proliferation, apoptosis, migration, and invasion, contrasting with low expression levels in normal breast tissue [72].

2.4. miR-141

Lutful et al. using a quantitative polymerase chain reaction strategy in cell lines from female dogs diagnosed with spontaneous mammary carcinomas or adenocarcinomas, demonstrated that miR-141 is a strong oncomiR, belonging to the miR-200 family [61]. Significant levels of miR-141 expression are strongly associated with highly aggressive breast carcinomas (grade III) compared to grade II breast cancer [73].

2.5. miR-429 and miR-200c

In both breast cancer and canine mammary tumors, specific miRNA groups have been identified with both overexpression and underexpression patterns. Notable miRNAs include miR-9, miR-155, miR-200a/b, and miR-429, which are overexpressed, while miR-1, miR-133a/b/c, and miR-214 are underexpressed in canine cell lines such as CMT12, CMT27, and CMT228. MiR-429 and miR-200c exhibit strong expression levels, targeting the ERRFI1 mRNA and acting as oncomiRs in canine mammary tumors, with fold increases over 1000 and 100-150 respectively [61].

In human breast cancer, miR-429 exhibits both overexpression and underexpression patterns, serving as an oncomiR particularly in cases with HER2+ amplification, driving tumor cell proliferation and migration. Conversely, miR-200c acts as a tumor suppressor, inhibiting cell proliferation and metastasis, particularly in triple-negative breast cancer. These miRNAs play significant roles in tumorigenesis and tumor progression, making them robust biomarkers in both human breast cancer and canine mammary tumors [74].

2.6. miR-497

At the level of canine animal cell lines, members of the miR-497 family (miR-497, miR-195, miR-15 and miR-16) are down-regulated, this regulation being also found at the level of CMT1211 and CMT7364 cell lines compared to the primary lines from canine mammary gland cells. The overexpression of miR-497 causes inhibition of cell proliferation and migration and the increase of apoptosis in the CMT1211 and CMT7364 cell lines [75].

Thus, miR-497 has been suggested as a diagnostic biomarker and therapeutic target in CMT. These aspects are consistent with those encountered in the case of HBC, where miR-497 is found among the least expressed oncomiR [76].

Overexpression of miR-497 resulted in inhibition of cancer cell proliferation, migration, invasion,

metastasis and cellular angiogenesis or cell cycle causing apoptosis by targeting Bcl-2-like protein 2 (Bcl-w), B-cell lymphoma 2 protein (Bcl-2), yes-associated protein 1 (YAP1), HIF-1α or cyclin E1 mRNAs [77,78].

2.7. miR-10b, miR-101, miR-125a/b, miR-136, miR-145, let-7f and miR-203

Some miRNAs play an important role in the metastasis process compared to the process of malignant transformation, being represented by miR-10b, miR-101, miR-125a/b, miR-136, miR-145, let-7f and miR-203. High levels of expression were identified in a metastatic group compared to non-metastatic or benign CMT [79,80].

The expression levels of miR-10b, miR-125b, miR-136 and let-7f gradually increase from normal breast tissue to benign tumor tissue and non-metastatic malignant tumor tissue to metastatic tumors [79]. The expression of miR-143 from non-metastatic CMT [66] from the canine SNP cell line identified by Osaki [81] was 1547.9 times higher compared to normal mammary gland tissue. MiR-203 expression was also downregulated in benign tumors compared to a healthy control group [79].

2.8. miR-210

MiR-210, increases in expression during the progression of malignancy resulting from hypoxia and has an important role in the metastasis process, through intensified angiogenesis [82].

Overexpression of miR-210 was observed in canine neoplasms compared to a control group [83]. In the case of HBC, miR-210 correlates with lymphonodal metastasis, clinical staging, differentiation, and unfavorable prognosis in patients diagnosed with breast cancer. Thus, miR-210 represents a potential prognostic biomarker of HBC and CMT [84,85].

2.9. miR-138a

MiR-138a represents the tumor suppressor gene, which shows significantly low values in the canine SNP cell line (0.007 times). This miRNA represses the epithelial-mesenchymal transition (EMT) determining the aggressiveness of cancer and its metastasis, representing a potential biomarkers in CMT [81].

2.10. miR-8832, miR-96 and miR-149

With the help of the genome-wide methylation process in CMT, a new miRNA, cfa-miR-8832, was identified, which is associated with both CMT and HBC [86].

Jeong et al. has also identified two genes: cfa-miR-96 and cfa-miR-149, which are over- and under-expressed, being associated with HBC, where they determine the proliferation, migration and invasion of cancer cells by reducing the target gene PTPN9 (the gene for non-receptor tyrosine-protein phosphatase type 9) [86,87].

MiR-149 is the tumor suppressor gene, which contributes to tumor progression, by supporting the aberrant activation of Rac [88] and the recruitment of macrophages to the tumor [89]. Both genes were conserved both in HBC and CMT, representing potential biomarkers [86].

2.11. Circulating miR-18a

RNA sequencing showed increased serum level of miR-18a (1.24 times), in the case of CMT, its values significantly differed between dogs with benign CMT and dogs with malignant CMT [90]. High levels were identified in a group of canine patients in which tumor metastasis was present at the lymphnodal level, compared to a group in which lymph node metastasis was absent, with miR-18a being proposed as a representative biomarker for HBC.

MiR-18a was also identified in the case of cell lines derived from breast cancer MCF-7 and MDA-MB-23, in which ER expression, decreased sensitivity to tamoxifen and endocrine resistance correlated with high miR-18a expression [91]. This was also overexpressed in breast cancer cell lines, such as MCF7 and ZR-75-1 [92]. Regulation of miR-18a in the case of healthy contralateral breast tissue and benign biopsy samples before the development of breast cancer, classifies the gene`s overexpression as an early tumorigenesis factor [93].

2.12. Circulating miR-19b

In both cases of humans and the canine animal model, the miR-19b biomarker plays an important role in diagnosing patients with different tumor types, including breast tumors. Currently, studies on invasive mammary cell lines attest to the fact that miR-19b favors tumor progression [94,95].

2.13. Circulating miR-21 and miR-29b

MiR-21 expression was upregulated in malignant and benign tumors compared to control samples, while serum miR-29b was significantly reduced, in malignant and benign groups compared to the control group [65].

Thus, miR-21 is a potential non-invasive prognostic biomarker for the early detection of CMT, and miR-29b is representative for the accuracy and sensitivity of a diagnosis, being evaluated together with miR-21 [65,96].

2.14. Exosomal non-coding RNAs (ncRNAs)

Exosomal non-coding RNAs, measuring 20-22 nucleotides, show potential as cancer prognosis biomarkers in carcinogenesis. They play a role in breast tumor diagnosis by regulating gene expression [62,97].

Specific miRNAs like miR-143 and miR-138a vary between canine mammary tumor cell lines and normal tissue. In malignant tissues, miR-210 and others are upregulated, including in metastatic biopsies [66]. Minimally invasive diagnostics reveal elevated miR-214 and miR-126 levels in serum from dogs with mammary carcinoma and other cancers [98].

Exosomal miRNA profiles differ between CMT cell lines and normal cells, linked to oncogenic pathways. These findings shed light on canine breast cancer

pathology and offer new diagnostic avenues for veterinary cancers. Comparative analysis with human models may validate shared biomarkers and pathways.

2.15. ExomiR in canine mammary tumor (CMT)

In canine mammary tumor-derived exosomes, miR-126 and miR-214 serve as biomarkers, influencing cancer pathogenesis by regulating processes such as angiogenesis, proliferation, migration, and cell death [99]. Changes in their expression significantly impact tumor progression, making them representative markers for CMT. Several miRNAs are upregulated both in canine mammary tumor cells and their exosomes, including miR-18a, miR-19a, miR-29b/c, miR-181a/b, miR-215, miR-345, miR-371, and miR-1841 [61,90].

Fish et al. identified exosomal miRNAs present in both CMT and HBC, such as cfa-miR-18a, cfa-miR-20b, cfa-miR-21, miR-29b, miR-93, cfa-miR-101, cfa-miR-105a, cfa-miR-130a, cfa-miR-200c, cfa-miR-340, and cfa-miR-486 [100].

These findings suggest their potential utility as non- or minimally invasive biomarkers for profiling CMT and HBC, offering significant implications for translational research.

Treatment of canine mammary cancer

In both human patients and canine counterparts, staging of breast cancer is crucial prior to initiating any treatment. This typically involves blood sample collection, chest and/or abdominal radiographs, and cytological evaluation of biopsy samples. Surgical methods, such as lumpectomy or total mastectomy, are the most common treatment options for canine breast cancer. Additionally, ovario-hysterectomy, performed concurrently with mastectomy, has been shown to improve survival rates, particularly for ER+ tumors and patients with high serum estrogen levels.

Chemotherapy, utilizing various chemotherapeutic agents, is another treatment modality for canine mammary tumors, akin to its use in other cancers. Multimodal therapy, which may include neoadjuvant chemotherapy and/or radiation therapy before mastectomy, aims to improve overall and disease-free survival rates.

While hormone therapy is a prevalent treatment option for ER+ breast cancer in humans, its application in canines has yielded mixed results. Anti-estrogen therapy can induce significant side effects in dogs, including vulvar swelling, vaginal discharge, and pyometra.

In canine models, surgery remains the primary approach for controlling mammary tumors, with the primary goal being the removal of tumors with clean resection margins to prevent recurrence. The type of mastectomy performed depends on factors such as tumor size and location. Adjuvant therapies, including chemotherapy, radiation therapy, and targeted therapy, may also be administered post-surgery to reduce the risk of recurrence and metastasis. Advanced metastatic cancer (stage IV) or inflammatory cancer (IMC) may not be amenable to surgical excision, in which case alternative treatment options are considered.

Conclusions

Breast cancer poses a significant global challenge, driving ongoing research in prevention, diagnosis, treatment, and prognosis. Real-world data aid in discovering new biomarkers for therapeutic targeting and patient stratification based on molecular subtypes. Comparative research between human and canine breast cancer models reveals shared epidemiological, clinical, and biological traits, essential for studying molecular signaling and immunomodulation.

Canine models, with spontaneous tumor occurrence and intact immune systems, offer advantages over rodent models. Similarities in tumor biology, prognosis, and response to therapy make canine models valuable for translational research, particularly in genomic approaches to identify new variants associated with breast tumors.

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