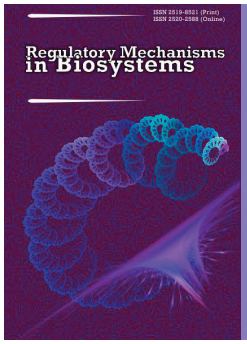

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A modern look at the molecular-biological mechanisms of breast tumours in dogs

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High morbidity and increase in the number of registrations of breast tumours in dogs, their wide application as biological models, discussion of numerous questions of oncogenesis, and the lack of a uniform/unified methodological approach to the study of molecular and biological mechanisms of treatment of cancer determine the relevance of the problem of cancer both in humans and in our domestic companions. The analysis of publications allowed us to establish the following patterns of carcinogenesis. The peculiarities of the biological behaviour of breast tumours depend on their pathomorphological structure. Genetic predisposition to breast cancer is characteristic only in the single breed aspect. Environmental factors are of critical relevance to carcinogenesis : chemical pollutants initiate oncogenesis indirectly – by altering the expression of several receptors, impaired endocrine balance and direct mutagenic effects. Reproductive status plays a key role in the initiation and progression of breast tumours by reducing the expression of estrogen, progesterone and prolactin receptor genes. The inflammatory response that accompanies the neoplasia process is characterized by increased production of cytokines, cyclooxygenase-2, interleukins (IL-1, IL-6, IL-8), vascular endothelial growth receptors, and impaired hemostatic status (oxidative stress), which promotes progression of disease. In breast cancer in dogs, genomic instability leads to genomic aberrations, and subsequently, mutations that support the proliferation, survival and dissemination of neoplastic cells. The initiation and progression of mammary gland tumours is provided by cancer stem cells by disrupting the regulation of precursor cell self-renewal, which also predispose to resistance to chemotherapeutic agents, radiation, and hormonal cancer therapy. The analysis of the publications revealed the major markers of carcinogenesis that could potentially be used as biological targets for the design of modern diagnostic strategies and high-performance therapeutic protocols.

Keywords: neoplasms; dogs; pathogenesis; markers of carcinogenesis; therapeutic targets.

Introduction

Breast neoplasms represent one of the most common oncological diseases, which gives relevance to their research in both human and veterinary medicine (Grüntzig et al., 2016; Bomko et al., 2018; Mysak et al., 2018; Klosova et al., 2019). In this case, the incidence of breast tumours can reach 70% of all reported cases of cancer (Merlo et al., 2008). According to a report by the International Agency for Research on Cancer, based on the Globocan cancer incidence and mortality rate, in 2018, the breast cancer incidence rate ranks second (11.6% of total cases) and the first among women, being the main cause of death (Bray et al., 2018). The advantage of using dogs as a biological model for the study of pathogenetic mechanisms of mammary tumours that pose a serious threat to human and dog health, primarily due to metastasis of the primary focus, against the background of insufficient study of their molecular mechanisms, has been demonstrated (Hawai et al., 2013).

With advances in molecular and cell biology, studies with cell systems have provided important conceptual advances for a better understanding of the mechanism of carcinogenesis, and animal models, by presenting tissues and systemic contexts of oncogenesis, serve to validate molecular assumptions and target possibilities in treatment and prevention. With the development of genetically engineered mouse models, the functional consequences and dynamics of genetic changes in tissues can be determined according to the stages of carcinogenesis. Cooperative models linking cell culture methods and relevant animal models offer simple quantitative approaches to assess the oncogenic potential of carcinogens and immunity, as well as the role of individual potential "candidates" in cancer genes in mechanisms of its development (Kulesz-Martin et al., 2018).

Not only are non-neoplastic lesions associated with tumour cells, they are complex "ecosystems" that involve a large number of different cell types and extracellular factors and are cascaded by interrelated reactions (Valkenburg et al., 2018). The biological complexity of human tumours necessitates the use of experimental models that are as similar as possible to the biology of human carcinogenesis. Domestic animals have characteristics (epidemiological, biological, clinical) that fill the gap between *in vitro* and *in vivo* studies, which are important for understanding the molecular aspects of human cancer (Pinho et al., 2012). The optimal selection of the dog as a biological model for the differentiation of genetically induced susceptibility to breast cancer and environmental exposure is associated with the genetic diversity of its breeds (Arnesen et al., 1995). In recent decades, there have been a number of reports regarding the clinical and molecular similarity of breast tumours in humans and dogs that allow the identification of prognostic factors, primarily at the molecular level, for use as therapeutic targets. In this case, breast neoplasia mimics cancer in humans, as evidenced by the similarity in overexpression of steroid receptors, proliferation markers, epidermal growth factor, p53 suppressor gene mutations, metalloproteinases and cyclooxygenase (Abdelmegeed & Mohammed, 2018).

Currently, there are many reports on the mechanisms of neoplasia development, but the lack of a unified methodological approach and the diversification of studies due to the discussion of many issues of pathogenesis in the absence of analysis and consistency of the obtained results hinders us from approaching a solution to the problem of improving the

effectiveness of treatment and prevention of cancer. In oncology, the focus is on personalization based on the use of genomic data to determine the risk of developing the disease, selecting effective diagnostic and treatment regimens, and predicting the likelihood of recurrence (Chute & Kohane, 2013). However, despite the proven feasibility of using dogs in such studies (Davis & Ostrander, 2014), the available information does not reflect the main links of their involvement in oncogenesis. Despite the complexity of the cytogenetic study of dog cells, due to the peculiarities of their complete karyotype, the analysis showed the similarity of clonal chromosomal aberrations in humans and dogs, which can be used as diagnostic and prognostic markers (Reimann-Berg et al., 2012). The "strengths" of dog models for the study of genomic associations will provide significant advances in oncology and a rapid transition to functional research (Alvarez, 2014).

Studying the biology of breast tumours in dogs, especially the molecular "events" associated with proliferation, cell survival, invasion and metastasis, is crucial for the development of effective therapies and strategies (Matos & Santos, 2015). To achieve this, veterinarians and geneticists from 12 European countries have launched a LUPA project that identifies mutations for four monogenic diseases that have been used to detect genomic changes in humans. However, further studies should lead to a better understanding of the molecular mechanisms of disease in humans and dogs (Lequarré et al., 2011). In order to summarize information on the biology of breast cancer in dogs for breast cancer in dogs and their "critical" evaluation, a comparative concept of "Single Health" has been proposed (Raposo et al., 2017).

Interdisciplinary research in comparative oncology combines scientific results in human and veterinary medicine and offers a unique opportunity to further analyze the mechanisms of development and progression of breast cancer, as well as to use them in identifying current areas of further research that will be useful to both humans and individuals and animals (Schiffman & Breen, 2015).

Thus, publications on the biology of breast tumours in dogs are presented, in most cases descriptive in nature and based on different methodological approaches, which makes it impossible to determine the general patterns of neoplasia pathogenesis. Therefore, it is important to analyze the available results of carcinogenesis studies to understand the mechanisms of appearance and development of breast tumours in dogs, as well as to identify targets for their effective therapy, based primarily on the proven multiple pharmacological resistance of neoplasia cells (Pawłowski et al., 2013). In Ukraine, however, the issue of the pathogenesis of breast tumours has not been sufficiently studied, and the research reports are scattered and limited mainly to the description of clinical and pathomorphological and biochemical disorders, which is insufficient to understand the essence of the mechanism of initiation, development and metastasis of cancers in dogs.

Given the insufficient study of the biology of breast tumours in small pets, the aim of the study was to analyze and summarize the results of current studies on the pathogenesis of breast tumours in dogs to identify new strategies for prevention and treatment of this disease.

Clinical and ecological aspects of biology of breast neoplasia in the bitches

The problem of neoplasms of the breast is currently relevant in both human and veterinary medicine, which accounts for the considerable amount of research in this direction. They are of particular importance given the advisability of using dogs as biological models for the study of cancer. The etiological and pathogenetic versatility and complexity of the mechanism of oncogenesis has given rise to numerous publications, but the presented results do not always have prognostic value, which limits their use in clinical practice.

The analysis of research directions of the problem of breast tumours indicates the continuation of the study of epidemiological and clinical and pathomorphological features of carcinogenesis, the role of environmental factors in the mechanisms of initiation and development of neoplasia, the results of which supplement the available information, but need detailed assessment. The most promising area in oncology is the study of gene mutations, which are the direct cause of the initiation of processes of carcinogenesis. However, against the background of the high activity of studying the genome for cancer, a considerable number of questions remain debatable. In addition, such studies are complex, require high-cost equipment, so they have not yet received significant clinical distribution.

Therefore, in this review, we have summarized the results of studies concerning the effects on carcinogenesis of age, breed factors, pathomorphological structure, reproductive status and environmental factors, and disorders of genome structure.

The basis of the analysis of biological features of breast tumours and the prediction of their "behaviour" is formed, first of all, by the results of epidemiological studies, which allow us to establish clinical signs, age and breed susceptibility to the disease, as well as their correlation with pathomorphological structure, reflecting the level of malignancy. Epithelial neoplasms were most commonly diagnosed in purebred dogs of small and medium breeds (Poodle, Cocker Spaniel, German Shepherd) of the older age group (9–12 years) with correlation of these indices with malignancy against the background of increasing morbidity over the last four years (Salas et al., 2015). Predictive significance of overall survival factors common to humans and dogs: size greater than 20 mm, positive nodal stage, III histological grade, lack of estrogen receptors and epidermal growth factor (ERα- and EGFR-negative status), high proliferation index, similarity of tumour biology in both cases. A short natural history of spontaneous invasive breast cancers and high rates of cancer-related mortality make it possible to complete preclinical studies quickly (Nguyen et al., 2018).

The relationship of the increase in the development of the breast tumour according to the clinical classification of TNM with the deterioration of the prognosis has been proved: the increase of the level of invasion into the surrounding tissues and vessels decreased the survival of the patients. The lifetime survival of animals with metastases to regional lymph nodes (category N_1/N_2) or distant metastases (category M_1) is significantly lower than in patients with local lesions (Yamagami et al., 1996). The above information is consistent with our previous studies: an increase in the size of breast tumours in dogs is accompanied by an increase in blood coagulation potential against the backdrop of a clotting factor deficiency, which indicates an increased aggressiveness of neoplasia and a worsening prognosis. The progression of haemostasiological equilibrium in the event of an increase in neoplasia is mainly due to the overactivation of the extrinsic coagulation pathway, which is triggered by a tissue factor, although at the same time, there is an increase in the imbalance of the internal coagulation mechanism associated with endothelial function (Bely et al., 2019).

Despite reports of pronounced age and pedigree susceptibility to the development of breast tumours: there is a higher likelihood of malignant neoplasia in purebred animals, compared to Metis, especially up to 7 years of age, primarily among Samoyed, Doberman-pinschers, Schnauzers, Yorkshire Terriers, although, with the maximum incidence rate among 8–13 year olds (Vascellari et al., 2016), in the absence of a unified methodological approach and a unified base, this issue remains debatable, which is related to a significant difference in distribution of individual breeds in certain territories. In particular, Egenvall et al. (2005) estimate the risk of breast cancer in English Cocker Spaniel and Doberman-pinscher 65 times higher than in the Collie, while Panchkhande et al. (2019) indicate the highest incidence rate (38.8%) in Metis. At the same time, Litterine-Kaufman et al. (2019) focus on a single mechanism for the development of breast neoplasia, regardless of age, reproductive status and multiplicity. The authors verified benign neoplasms in 85%, malignant – 15%, non-neoplastic lesions – 5% of cases against the background of significantly higher frequency of registration of malignant types in the first – fourth mammary set. Against the background of the proven multifactorial neoplasia process, recent studies in purebred populations indicate genetic aspects of breast tumour development (Dobson, 2013), which is consistent with the results of population genetic analysis of structural variations in this pathology, which is important for the genetic analysis of phenotypic and behavioural variations (Nicholas et al., 2011).

Genetic heterogeneity among isolated groups of dogs within the breed causes a lack of confidence, and variants of susceptibility to breast

cancer within known genes explain only a small fraction of "family" cases. Therefore, an alternative is the study of pedigree, since artificial selection provides a homogeneity that can be used to investigate breast cancer research strategies in humans (Goebel & Merner, 2017). In particular, Rivera et al. (2009), based on a well-established association of BRCA1 ($P = 0.005$) and BRCA2 ($P = 0.0001$) genes with mammary tumours, reported genetic susceptibility in Cocker Spaniels with more pronounced dependence of malignant types on BRCA2, and Borge et al. (2013) established associations of this disease with the estrogen receptor 1 gene (ESR1), which showed a high degree of confidence between the groups with high and low risk of developing the disease ($P_{Bonf} = 0.021$).

The biological behaviour of carcinomas in mixed breast tumours depends on their epithelial histological subtypes: category T_3 is more commonly associated with carcinosarcomas, T_1 and T_2 are benign mixed tumours and carcinomas in mixed tumours. Most females with benign mixed neoplasia have stage I, 92% of animals with carcinomas in mixed tumours are stage I–III, while 8% are stage IV–V; 70% of patients with carcinosarcomas have stage I–III, and 30% have stage IV–V (Nunes et al., 2019). In bitches with adenoma and carcinoma of the breast significantly higher expression of epidermal growth factor receptor (HER2) mRNA 2 is exhibited compared to normal mammary glands, but in the absence of a significant difference between benign and malignant neoplasms (Burrai et al., 2015). The histological subtype has an effect on estrogen receptor (ORα) and progesterone (PR) expression: simple and complex adenomas, as well as simple tubular carcinomas, exhibit the highest levels of expression, whereas malignant myoepitheliomas and solid/anaplastic carcinomas are minimal (Kim et al., 2014).

Progression and metastasis occurs as a result of a complex multistage molecular cascade, some of which are linked by adhesive interaction, invasive processes, and response to chemotactic stimuli. Among them, Brooks et al. (2010) highlight, first of all: tumour angiogenesis; disaggregation of neoplasia cells from primary tumour tissue mediated by cadherins and catenins; invasion and migration through the basement membrane and extracellular matrix surrounding the epithelium of the neoplasm with subsequent spread to the endothelium of regional blood vessels, mediated through integrins and proteases; intravasation of tumour cells into blood vessels to hematogenous dissemination into distant sites, adhesion of circulating cancer cells to endothelial mucosa in the capillary channel of the target organ.

Hypoxia promotes impaired tissue integrity by increasing N-cadherin expression, which allows cancer cells to avoid anoikis. By increasing the expression of plasminogen activator urokinase-type hypoxia, it enhances proteolytic activity, thereby causing cell invasion through the basement membrane and stroma with subsequent migration of tumour cells into the blood and lymphatic channels, as well as angiogenesis and lymphanginesis in primary neoplasia by induction of endothelial growth factor (Sullivan & Graham, 2007).

Significant diversity (genetic, cytogenetic, epigenetic and phenotypic) exists within categories and between tumours, but the causes of these changes, as well as their consistent hierarchical structure between organs, have not yet been well understood. These phenomena are partly explained by the evolutionary ecological theory of organs, according to which unfavourable environmental conditions form the levels of mutations and polymorphism in the body. Organs in the body can be regarded as specialized ecosystems that are more or less effective for the suppression of neoplasms for ecological and evolutionary reasons. When a malignant tumour develops in an organ that causes pronounced selection pressure on neoplasia, its cells are expected to exhibit a wide range of survival strategies from hypermutator phenotypes (high mutation frequency and significant diversity) to poorly variable, invisible to natural occurring defences (Giraudeau et al., 2019).

There is considerable scientific interest in the possible role of environmental pollutants in the etiology of breast neoplasms, especially regarding chemicals that directly or indirectly affect living creatures, in particular animals. According to the studies of Andrade et al. (2010), the level of contamination of adipose tissue around tumours by substances such as alletrin, cyhalothrin, cypermethrin, deltamethrin and tetramethrin reaches 33.3%, on the basis of the direct dependence of the aggressiveness of neoplasia on their content. Based on the study of carcinogenic properties of chemicals in rats, their direct involvement in the activation of tumour mechanisms by enhancing cell division has been proven (Gold et al., 1998).

There is increasing evidence from epidemiological studies indicating the role of toxicants found in everyday products in the mechanisms of tumour cell transformation (Rodgers et al., 2018). They have been shown to increase the likelihood of breast neoplasia by inhibiting functional differentiation, impaired endocrine balance due to changes in levels, metabolism and transport of hormones in the blood and tissues, and the expression of their receptors (Fenton, 2006). Endocrine disorders with the development of breast tumours have been shown to cause more than 10,000 chemical substances (Teitelbaum et al., 2015).

The expediency of using dogs as a biological model to determine the role of the chemical influence of the environment on the mechanisms of carcinogenesis, including pollutants of the dl-PCB family (PCB-118, -156, -105, -114) has been shown, which indicate the fundamental role of the aryl carbohydrate receptor cascades of breast cancer (Sévère et al., 2015).

The development and progression of breast cancer can be affected by adipose mesenchymal adipose tissue (ADMSC) cells that are sensitive to the carcinogen of benzo(a)pyrene (BaP) in the environment by enhancing the expression of the AhR signaling pathway, suppressing the expression of AhR, suppressing proliferator (PPARγ) during adipogenesis (Rathore & Cekanova, 2015).

The combined effect of a combination of several heavy metals: antimony (odds ratio [OR]: 1.8, 95% confidence interval [CI]: 0.9, 3.7, P-trend: 0.05), cadmium (OR: 2.3, 95% CI: 1.2, 4.4, P-trend: 0.04), cobalt (OR: 2.0, 95% CI: 0.9, 4.4, P-trend: 0.04), which are in the air, may cause associations with neoplasm receptor status for ER/PR-negative breast cancer (Kresovich et al., 2019), the content of which is highly reliable is a marker of predicting the risk of the disease (White et al., 2019).

A possible cause of the initiation of the mechanism of breast neoplasia is mycotoxins, which are found in all types of dog food, regardless of their quality: aflatoxin B_1 ($P = 0.0356$, $OR = 2.74$, 95%), aflatoxin G_1 (AFG1) ($P = 0.00007$, $OR = 4.60$, 95%), aflatoxin G_2 (AFG2) ($P = 0.0133$, $OR = 9.91$) (Frehse et al., 2015).

Estrogen-like chemicals, in contrast to non-estrogen xenobiotics, in addition to their chemical properties, cause estrogenic action, increasing the load on their natural level in the body. At higher doses, natural estrogens and chemicals that have similar characteristics cause adverse effects. In addition to the estrogenic effects, estrogenic environmental chemicals cause multiple genetic or non-genetic disorders: the products of nuclear redox reactions (DES) alter the transcriptional regulation of proteins and DNA; transcription is inhibited; tyrosine phosphorylation of nuclear proteins, including RNA-polymerase, p53 and nuclear insulin-like growth factor receptor I; DNA-polymerase gene transcripts of the DNA repair gene are reduced and mutated (Roy et al., 1997).

Although limited and mixed, experimental evidence to date proves the role of conventional chemicals as key target molecules of immune and non-immune cells that are mechanically associated with immune-associated immune responses, neoplasia invasion, and metastasis through a number of cells not all of which cause an inflammatory response (Thompson et al., 2015).

The role of reproductive status in the mechanisms of carcinogenesis is well known, but views have changed somewhat. Recent studies indicate an underestimation of the importance of prolactin in the development and progression of breast tumours: it acts as a promoter of benign and malignant neoplasms, both *in vitro* and *in vivo*, against the similarity of mechanisms of stimulation of carcinogenesis in humans and dogs (Michel et al., 2014). The above information is consistent with a better prognosis for ovarian hysteroectomy, which reduces mortality by 33% against a prolongation of the average life expectancy of 17 months by preventing breast cancer and pyometra, with mortality rates of 37% and 7%, respectively (Waters et al., 2017). However, the limited data available and the risk of bias in the published results lead to insufficiently high levels of their reliability, which makes it impossible to recommend ovariohysteroectomy for introduction, and this issue needs further investigation. Of the eleven reports in peer-reviewed English-language publications on the relationship between sterilization and risk of breast

tumours, nine were rated by authors as having high levels of bias and four as moderate (Beauvais et al., 2012). In particular, Morris et al. (1998) indicate that there is no effect of prevention of breast tumours on the background of sterilization of bitches and the likelihood of 26% of cases of their development in other packages of benign types, as well as a mortality rate of 63% for malignant neoplasia over two years (in non-malignant animals 57%).

In vivo studies have shown that estrogens, progesterone and prolactin control different stages of breast development, which proves their role in the development of breast tumours. In particular, the two progesterone receptor targets, the NfkB and Wnt4 receptor ligand activators, serve as paracrine mediators of progesterone receptor-induced stem cell proliferation and activation (Brisken et al., 2015).

Endogenous progesterone and synthetic progestins can cause hypersecretion of growth hormone "breast" origin, hyperplastic ductal changes in the mammary gland and the development of cystic endometrial hyperplasia in dogs, as evidenced by a decrease in the expression of PR gene in uterine tissues against the background of treatment of patients with acetate medroxyprogesterone (Bhatti et al., 2007).

Hormone receptor expression is significantly reduced in malignant breast tumours, compared to non-neoplastic tissue and benign neoplasia. Among histological subtypes, minimal expression levels of estrogen receptor genes (ESR1), progesterone (PGR), and prolactin (PRLR) have been established in solid, anaplastic, and ductal cancers (Mohr et al., 2016). Canadas-Sousa et al. (2019) identified genetic profiles, in particular ESR1 (rs397512133, rs397510462, rs851327560, rs397510612, rs852887655, rs852684753, rs852398698) associated with the later development of neoplasms of lactic pathology: significant tubular differentiation, and low dog-adjusted prognostic index (vet-NPI).

Dogs have advanced breast cancer classification based on EGFr c-bbB-3 and c-erbB-4 gene expression, and identify new expanded phenotypes that go beyond the traditional human-baseline luminal-baseline characteristics. Quantitative analyses have been developed and validated to evaluate the phenotypes of mammary gland malignancies based on human-like ER1, PR, and c-erbB-2/HER2 receptors, as well as evaluate the role of relatively poorly understood c-erbB-3 and c-erbB-4 in each of the neoplasia phenotypes (Kabir et al., 2017).

The involvement of the inflammatory response in the mechanisms of initiation and development of the neoplasia process is demonstrated, as evidenced in such patients by significantly higher concentrations of acute-phase proteins, in particular haptoglobin ($P < 0.043$) and C-reactive protein ($P < 0.008$), compared with clinically healthy animals, but in the absence of their diagnostic and prognostic significance, due to a wide range of variations (Planellas et al., 2009). These changes in the markers are caused by metastasis, significant tumour size, secondary inflammation and ulcerative process. However, in animals with breast neoplasia a significant increase in positive acute-phase proteins has been found in the presence of metastases, ulcers and sizes larger than 5 cm, C-reactive protein in patients with comorbidities, indicating that the acute-phase response is stimulated by factors such as dissemination cells, primary foci size, tissue necrosis, and secondary inflammation (Tecles et al., 2009).

The list of signaling molecules that are released by inflammatory cells and serve as tumour growth effectors is constantly updated and increasing: cyclooxygenase-2, epidermal growth factor (EGF), angiogenic growth factor (VEGF), chemokines, cytokines, etc (Carvalho et al., 2016). Confirmation of the role of inflammation in oncogenesis of breast tumours in bitches by enhancing angiogenesis is an increase in the expression of cyclooxygenase-2 and vascular endothelial growth factor (VEGF) in the case of malignant disease compared with benign (Queiroga et al., 2011), and also a direct correlation with its intensity, in particular in all cases of inflammatory carcinoma (IMC), compared with non-inflammatory cancer, recording a statistically significant increase in the expression of VEGF and the percentage of VEGF immunoreactive cells ($P = 0.02$), but in the absence of a difference between them in express receptor HER2 (Millanta et al., 2010).

In the non-inflammatory nature of the carcinoma, immunoexpression of cyclooxygenase-2 is significantly associated with vascular growth factor A (VEGF-A), in inflammatory VEGF-D (the lymphogenic pathway), its VEGFR-3 receptor, and lysophosphatidylinositol (LPI), which allows us to presume the stimulatory role at stimulus of the lymphogenous pathway due to the specific role of cyclooxygenase-2 in angiogenesis of breast tumours (Clemente et al., 2013).

Malignant tumours are often associated with a relatively high number of infiltrating lymphocyte (TIL) tumours, BRCA1 gene expression, and local production of cytokines that play a role in carcinogenesis. In particular, mammary neoplasms of the mammary gland are three times more infiltrated with T-lymphocytes, compared with B-cells, against the background of the correlation between expression of interleukin-1 and -6 and the likelihood of metastasis (Kim et al., 2010). Saeki et al. (2012) showed a significant excess of intratumour T-lymphocytes for malignant breast neoplasia in dogs, compared with benign ones, which substantiates a poor prognosis in patients. In particular, the authors found a statistically significant increase in the number of intra-tumoral T-lymphocytes (23.2 ± 23.8) in the group of malignant tumours, compared with the group of benign tumours (14.0 ± 16.0, $n = 89$; $P < 0.05$), as well as a correlation of high T-lymphocyte infiltration with poor prognosis in multivariate analysis ($P < 0.05$). The similarity has been described between human and canine breast cancer in relation to T-lymphocyte infiltration, the relationship of $CD4^+/CD8^+$ and T-cells with low survival rates and the stimulation of the progression of Th2-cell neoplasia, suggesting the development of spontaneous neoplasms in the context of the natural immune system and the ability to use dogs as a biological model for the study of immunological aspects of oncogenesis in humans (Carvalho et al., 2014).

Interleukins play an important role in carcinogenesis as potential modulators of angiogenesis, leukocyte infiltration and growth of tumours. Increased inflammatory response is accompanied by increased levels of interleukin-8 (IL-8) in the blood, as well as interleukin-10 (IL-10) in tumours, blood and tissues. In malignant tumours, the concentration of interleukin-6 (IL-6) exceeds the corresponding values for benign neoplasia and in healthy breast tissue, IL-8 only in relatively clinically healthy animals; in serum, the content of IL-1α and IL-8 is higher in malignant tumours compared with benign and control ones (de Andrés et al., 2013). Gelaleti et al. (2012) have shown a positive correlation of IL-8 with tumour progression, involvement of lymph nodes, recurrence and death, which is due to the close association with the metastatic phenotype of non-neoplastic breast cells.

Unlike malignant types of breast tumours with a mild inflammatory reaction, the pathogenesis of inflammatory cancer is characterized by a high risk of metastasis to the bladder and reproductive organs, low – in the lungs, liver and kidneys, with the exception of the possibility of lesions of the bones, which confirm the disease neoplasia (Clemente et al., 2010).

Cytokines released in the microenvironment of neoplasms play a major role in the pathogenesis of cancer, promoting the growth and progression of the process, as well as the regulation of antitumour response by the body. The function and significance of cytokines in neoplasms have not yet been well understood, although relevant data have been obtained in classic examples of comparative models of human cancers such as osteosarcoma, melanoma, breast tumours, and lymphoma. A deeper understanding of the cytokine signature may contribute to the diagnosis, prevention and treatment of the disease (Irac et al., 2019).

However, despite the chronic course of the disease, cytokines in the early stages of breast neoplasia, even in malignant type, are not able to cause disorders of hormonal homeostasis with hypothalamus-pituitary-adrenal and hypothalamus-pituitary-thyroid mechanisms (Salomão et al., 2018). Breast carcinomas in dogs are characterized, in comparison with clinically healthy animals, by an increase ($P < 0.05$) of cytokine levels (TNF-α, INF-γ, IL-1 and IL-6), nitric oxide, increased mechanism of protein oxidation and antioxidant activity that proves their association with oncogenesis (Machado et al., 2015).

Cyclooxygenase-2 is directly involved in the modulation of tumour progression within a dense microenvironment and contributes to the more aggressive behaviour of the microenvironment (Esbona et al., 2016), formed by enhanced stromal deposition of extracellular collagen, which is increased by malignancy. MMTV-PyVT neoplasms (artificially initiated mammary tumour virus – the antigen of the middle T-virus polyoma) that occur in dense collagen environments alter the expression of cytokines, including those involved in the maturation and recruitment of neutrophils – GM-CSF, PGDF-BB and IL-1α, compared with neoplasia developing in

a dense environment (García-Mendoza et al., 2016). Collagen, being a major component of neoplasm microenvironment and involved in cancer fibrosis, influences the behaviour of neoplastic cells through integrins, discoidin domain receptors and tyrokinases, as well as some signaling pathways. Hypoxia, widespread in collagen-rich conditions, exacerbates the progression of cancer, and other extracellular matrix substances: fibronectin, hyaluronic acid, matrix metalloproteinases by interacting with collagen affect the activity of tumour cells (Xu et al., 2019).

Studies indicate a pronounced similarity in the biology of tumour-associated stroma in cancers of dogs and breast tumours in humans, although there are some differences. In particular, an increase in Col1 α1 (collagen 1 α1), αSMA (smooth muscle alpha-actin), FAP (fibroblast activation protein), PDGFRβ (platelet-derived growth factor beta receptor), decrease CXCL12 (factor 1, obtained from stromal cells) against the background of no shifts in MMP2 (matrix metalloproteinase) and IL-6 (interleukin-6) (Ettlin et al., 2017).

Under conditions of acute-phase reaction, inflammatory and epithelial cells secrete reactive oxygen and nitrogen species that cause DNA damage, which in turn causes mutations and genome instability, inflammation in microenvironment tissues, including the formation of 8-oxo-7,8-dihydro-2-deoxyguanosine and 8-nitroguanine, which is characterized by hypoxia. The latter is the initiation of the synthesis and expression of factor and nitric oxide synthase, which increases the levels of intracellular reactive nitrogen species (RNS) and oxygen (ROS), thereby causing DNA damage and poor prognosis. In addition, tumour-induced inflammation induces nuclear factor B, leading to iNOS-dependent DNA damage (Kawanishi et al., 2017). In this case, the neoplasic process is in most cases characterized by aggressive "behaviour" due to damage not only to DNA but also to other biomacromolecules, in particular proteins and lipids, which leads to their dysfunction. In particular, oxidatively damaged transferrin releases iron ion, which can mediate Fentoma reactions and generate additional reactive oxygen species, causing dysfunction of antioxidant proteins and increased oxidative stress. Such disturbed structures of biomacromolecules can form a vicious cycle of oxidative stress, thereby initiating the development of cancer. Epigenetic changes, such as DNA methylation and disruption of miRNAs, play a vital role in carcinogenesis, especially in inflammatory cancers (Murata, 2018).

Gene mutations are a key factor in tumorigenesis

Recently, significant advances have been made in understanding the molecular mechanisms and critical pathways that drive the development of breast cancer in humans and dogs. Global gene expression profiling by 12 types of malignant mammary tumours revealed 1699 differentially expressed genes, and their involvement in tumourigenesis, recurrence, and metastasis has been proven (Varallo et al., 2019). Most of the differentially expressed genes are related to the functions and pathways of carcinogenesis and are related to the induction and maintenance of tumour progression: metastatic carcinomas have significant activation of genes that regulate the cell cycle, matrix modulation, protein clotting, and protease differentiation, growth pathways and regulation of actin (Klopfleisch et al., 2010).

Promising biomarkers that characterize the biology of neoplasms are mutations in the breast cancer gene 1 and 2 (BRCA1, BRCA2), Ki-67 antigen, endothelial growth factor receptor, epidermal human growth factor (HER2), estrogen, progesterone, and cygesterone, and cytogene proliferative cell nuclear antigen, p53 tumour protein, E-cadherin, vascular endothelial growth factor and circulating neoplasia cells. Despite numerous reports, the evaluation of biomarkers for breast tumours is not common practice, so further detailed studies are desirable, including vascular endothelial growth factor, cancer stem cells, circulating neoplasia cells, which can be used as a model for comparative oncology studies of breast cancer and testing therapeutic directions for the treatment of this pathology (Kaszak et al., 2018).

Recent studies indicate that epigenetic regulators and non-coding RNAs can play an important role in the development of breast tumours and contribute to heterogeneity and metastatic aspects of this pathology, primarily in triple-negative cancer. The neoplasia process in the mammary gland consists of a group of biologically and molecularly heterogeneous pathological disorders that develop in the functional tissue. Mutations in BRCA1 and BRCA2 genes are one of the immediate causes, but some cancers differ in primary locus (ducts, lobules) and invasiveness, and therefore have different prognosis and treatment outcomes (Feng et al., 2018).

Germline mutations in the BRCA2 neoplasia suppressor gene, interacting via BRC with RAD51, are an important component of the cellular mechanism for maintaining genome stability and repairing double strand breaks. Exon 11, the largest exon of the BRCA2 gene, encodes eight repeats of the BRC domain, remains the least studied. The authors have established in the tumour tissue of the mammary gland that there are 19 sporadically distributed point mutations, in particular, 68% are "false" and 32% are hidden (Hsu et al., 2010).

Genome instability and alteration of DNA damage repair pathways can cause the hypoxic state of neoplasia tissue. In this case, acute and chronic hypoxia leads to the initiation of various pathogenetic tumour mechanisms. Hypoxia can control a metastatic phenotype secondary to genetic instability, increased angiogenesis, decreased apoptosis, and activation of a number of genes involved in the metastatic cascade. It has different biological consequences, depending on changes in hypoxia-induced factor 1α-mediated transcription, the features of protein translation disorders, and differential activation of hypoxia-related major cell cycle elements. Under hypoxia, cells can acquire a mutant phenotype, which is based on a decrease in RNA repair, an increase in the frequency of mutations, and an increase in chromosomal instability (Bristow & Hill, 2008).

Support for the proliferation, survival or progression of cancer cells in various cellular stress conditions is supported by mitochondrial changes, which include: activation of oxidative metabolism and the use of alternative substrates and metabolites, increased production of superoxide, mutations in mitochondrial DNA, disturbance of their morphological structure and dynamics (Shoshan, 2017), which is caused by the Warburg effect (restriction of the admission of pyruvate glycolysis into mitochondrial oxidative metabolism), which allows tumour cells to avoid the over-generation of reactive oxygen species, thereby increasing their resistance to anoikis (a particular type of cell death that is a barrier to dissemination) and survival for metastasis. Accordingly, prometastatic HIF and Snail transcription factors attenuate oxidative metabolism, whereas p53 tumour suppressor and KISS1 metastasis suppressor promote mitochondrial oxidation (Lu et al., 2014).

Based on BRCA1, BRCA2 studies, which are associated with breast cancer risk factors in dogs, a high-quality genome sequence model has been created, as well as single-nucleotide polymorphism "maps" relevant for analysis of genomic association (Rivera & von Euler, 2011).

The data obtained by Klopfleisch et al. (2010) suggest that loss of transforming growth factor beta-3 (TGFβ-3) and binding protein-4 (LTBP-4) causes growth-promoting effects in tumours in the late stages, and loss of their expression together with decreased receptor expression TGFβ-3 (TGFβR-3) is an increase in the proliferative activity of breast neoplasia, which is similar to cancer in humans. In the early stages of breast carcinogenesis in dogs, there is a decrease in the expression of miRNAs of the p27 gene – a cyclin-dependent kinase inhibitor that delays the G1-S phase transition of the cell cycle, but in the absence of a significantly significant difference between malignancies. In this case, unlike the unchanged mammary epithelium, 91% of which exhibits nuclear expression of p27, it is established: for adenoma – in 22%, carcinoma – 20%, metastases to lymph nodes – 12% of cases.

MicroRNAs (miRNAs) play an important role in many biological pathways, the effects of which are the most common way of regulating genes after transcription. Comparative analysis of unregulated gene sets or cancer signaling pathways showed that in human and dog breast tumours a significant relative proportion of orthologous genes was increased. In particular, a group of cell cycle regulators – Cyclone Dependent Kinase Inhibitors (SKIs), which act as potent neoplasmic suppressors, are often defective in mammary gland neoplasms. Co-deletion or homozygous loss of the INK4A/ARF/INK4B locus (CDKN2A/B), which encodes three families of CKI tumour suppressor genes (p16/INK4A, p14ARF, and p15/INK4B) for many neoplasms, including cancer, suggest their important genetic order and localization in orthologous chromosomal regions (Lutful Kabir et al., 2015). Most cancers, including breast neoplasia, secrete exosomes into surrounding tissues and blood that

contain microRNAs (biomarkers of metastasis and tumour phenotype), thereby affecting biologically relevant hormone receptors and oncogenic pathways of biomarkers of metastasis and tumour phenotype (Fish et al., 2018). The most significant difference in miRNA expression is observed between metastatic and non-metastatic neoplasms, indicating its more important role in the process of metastasis than malignant transformation. However, despite the importance of differentially expressed miRNAs as potential markers of metastasis, the levels of cfa-miR-144, cfa-miR-32, and cfa-miR-374a are not predictive (Bulkowska et al., 2017).

The miRNAs involved in the initiation and progression of cancer in some neoplasms can be both activated and inhibited. In particular, miRNA-1 is involved in the proliferation and migration of stem cells in breast tumours, as evidenced by an increase in their number after inhibition of miR-1 expression in MCF-7 cells and a decrease in the background of active expression of miR-1 (Sahabi et al., 2018). A group of miRNAs comprising miR-21, miR-155, miR-9, miR-34a, miR-143/145, and miR-31 were found to be altered for breast and human cancers (Lutful Kabir et al., 2015).

Breast neoplasms by regulating miRNAs increase the expression of TGFBR1, TGFBR2, SOS1, CHUK, PDGFRA, SMAD2, MEF2A, MEF2C, and MEF2D genes, which are involved in the signaling of tumour necrosis factor β-factor stem cells on the background of their epigenetic difference from differentiated neoplasia cells (Rybicka et al., 2015).

Simple carcinomas of dogs are histologically similar to breast cancer in humans, have significant genomic aberrations, in most cases similar clinical features. Complex carcinomas of female dogs are characterized by cell proliferation – both luminal and myoepithelial, rarely registered for breast cancer in humans and without genomic anomalies, but in the presence of 35 genes of the following disorders: inhibition of chromatin, enrichment with active modification of histone H4-acetylation and depletion of repressive modification of H3K9me3 histones (Liu et al., 2014). Important in the mechanisms of oncogenesis is the high molecular heterogeneity of breast carcinoma in bitches, which shows an association of its stage and degree with survival in multidimensional regression, with no correlation between the molecular and histological subtype. In particular, most luminescent A and basal tumours were carcinomas of grade 1, whereas luminal Bs were grade 2–3 ($P = 0.009$). There were no differences in the percentage of molecular subtypes between simple and complex/mixed carcinomas ($P = 0.47$) (Sassi et al., 2010).

Genetic alterations of E-cadherin (CDH1) have been shown to influence the likelihood of breast cancer formation, progression, and biological behaviour in female dogs: rs850805755 and rs852280880 are associated with reduced risk and late onset of neoplasia, low carcinoma formation, and nuclear pleomorphism; rs852639930 – the formation of small tumours with non-infiltrative, non-invasive growth, indicating the protective role of genetic variants of CDH1 (Canadas et al., 2019).

Two single-nucleotide polymorphisms (SNPs) in the catechol-o-methyltransferase gene, which is responsible for the inactivation of catechin estrogens, a potentially carcinogenic metabolite, have implications for clinical and pathological features and disease outcome: rs853046495 rs23350589, rs23322686, rs23336579, and rs852564758 – development of medium or high histological grade carcinoma with vascular invasion; rs851328636 and rs853133060 – reduced nuclear pleomorphism and well-differentiated carcinomas (Canadas et al., 2018).

Associative analysis of criteria such as the classification of neoplasms, their size and the age of patients showed that structural genetic aberrations are more common in 7–8 year old dogs of large and giant breeds with malignant neoplasms of II and III degrees of mesenchymal origin (Surdyka et al., 2019). Compared to healthy specimens, genome copies are characterized by larger plot sizes and number of amplifications, and in some cases include genes with potential effects on tumour progression (Gurgul et al., 2014).

Despite reports of the role of genetic mutations in the pathogenesis of breast tumours, they are not associated with pathomorphological structure. Changes in exons 5–8 of the p53 gene suppressor were found in 11% of benign tumours and 25% of malignancies, indicating their probable initiation at early stages of carcinogenesis, but there is no evidence of their correlation with histological type (Muto et al., 2000). Brandão et al. (2013) against the background of the correlation between the amount of DNA damage and the aggressiveness of neoplasia, did not find statistical difference of DNA mutations for different types of breast cancer. The most common cellular and molecular processes involved in tumour progression are non-coding RNAs, epigenetic modifications, and immune responses. Among the 117 genes studied, only about 10% are estimated to be high risk factors for the initiation of carcinogenesis (Moghbeli et al., 2019).

In many breast cancers, multiple miRNA suppressors of tumours (miR-206, miR-17-5p, miR-125a, miR-125b, miR-200, let-7, miR-34 and miR-31) are observed to be lost and excessive expression of individual miRNAs (miR-21, miR-155, miR-10b, miR-373 and miR-520c). However, the strands organized by these miRNAs are largely unknown, although key targets contributing to the disease phenotype have been identified (O'Day & Lal, 2010).

An important link in oncogenesis, which is equally relevant for both humans and dogs, is the attenuation of genetic diversity, which is associated with the risk of inbred depression, which results in decreased growth rate, fertility, fertility and viability of offspring, as well as increased sensitivity to pathogens. However, the link between low genetic diversity or inbreeding and cancer is complex and needs further research, including genome-wide association studies in domestic and wild animals, population genetic and genomic analysis of species susceptible to tumours, epidemiological monitoring, which is needed to decipher such associations (Ujvari et al., 2018).

According to the modern theory of carcinogenesis, the initiation and progression of breast tumours are responsible for cancer stem cells (CSC) (Barbieri et al., 2012), which are a small subpopulation of cells similar to humans and dogs, identified by markers – CD44, CD133 thyroxykinase, an epithelial-specific antigen (Ranji et al., 2016), is characterized by a unique ability to self-repair and differentiation, providing tumour resistance to chemotherapy and radiation therapy (Rybicka & Król, 2016). The cancer stem cell hypothesis involves a violation of the regulation of self-healing pathways in precursor cells, which causes the development of neoplasms. Like human breast cancers, they contain CSC subpopulations in dogs, which, in a comparative oncological aspect, represent a valuable translational model of breast neoplasm initiation, growth, and metastasis to predict the effectiveness of anticancer drugs (Barbieri et al., 2015).

Breast tumours in bitches with more aggressive molecular subtypes are associated with the cancer stem cell phenotype. Basal subtype neoplasms had more CD44+/CD24 cells, resulting in a worse prognosis and indicating correlation with cancer stem cells (CD44, CD14, CD10, ESA, and MUC-1) (Figueroa et al., 2015).

Stroma plays an important role in the pathogenesis of breast tumours. A clear reprogramming of the stroma has been established even in the case of small benign breast tumours against the background of a significant difference between them and malignant tumours, with the key role of co-expressing genes, potential molecular drivers of this mechanism (Amini et al., 2019).

Proliferation, dedifferentiation, and migration of stem cells by breast tumours are regulated by sex steroid receptors (SSR), but the question remains of the role of classical hormonal biomarkers: alpha- and beta-estrogen receptors (ERα; ERβ) and androgen receptor (AR) in controlling the various ways of their transduction (Giovannelli et al., 2019).

Crucially important in the development of cancer is the effect of miRNAs on mammary gland neoplasia stem cells through the action of tumour oncogens and tumour suppressors, which may inhibit their invasion and metastasis, modulate clonogenicity and oncogenicity, and to regulate resistance to chemotherapy (Fan et al., 2017).

Stem cells for breast cancer play a critical role in acquiring resistance to endocrine therapy for estrogen receptor-positive (ER+) breast cancer as a result of complex changes including ER, growth factor receptors, Wnt/β-catenin, and microenvironment of neoplasm (Rodriguez al., 2019). The difference in expression of these markers explains the aggressive behaviour of neoplasia, higher recurrence rates and metastatic potential, but in the absence of their correlation with different cell populations. Poor ER expression in breast stem cells (BCSCs) may be a strategy for BCSCs to prevent the effect of hormonal therapy for ER+ cancer (Chopra et al., 2018). Cancer stem cells of dogs are characterized by their increased ability to form tumour spheres, predominantly expressing mesenchymal markers

on the background of greater invasiveness compared to parental cells, indicating their mesenchymal phenotype, and are relatively resistant not only to cytostatic and chemotherapy, but also ionizing radiation (Pang et al., 2011). The emergence and dissemination of malignant neoplasms are facilitated by two critical stem cell properties: their ability to self-renew and differentiate into unlimited heterogeneous cancer cell populations (Bao et al., 2013). That is, cancer stem cells are a unit of selection for clone therapy because they are insensitive to most treatments, including chemotherapy, radiation, and hormone therapy (Simões et al., 2015). However, there are reports proving the reverse effect of stem cells: inhibition of tumour growth occurs through the transmission of chemokines, modulation of apoptosis, vascular "support" and immune modulation, which substantiates the need for systematic research in this direction (Klopp et al., 2011).

In 20–30% of cases, breast carcinogenesis, tumour growth, and invasion are driven by overexpression of the HER2 gene due to the effect on normal and malignant stem cells, increasing their population and precursor cells, leading to increased aggression and metastasis. In particular, overexpression in individual breast cancer cell lines increases the proportion of cancer stem cells that express ALDH, which is exacerbated by mechanisms of oncogenesis and invasion (Korkaya et al., 2008).

That is, in the biology of cancer, mesenchymal stem cells exhibit contradictory aspects: on the one hand, they have features that give them the ability to support cancer cells under conditions of multifaceted protective reaction by the body, and on the other, due to the ability to penetrate the tumour tissue and secrete cytokines, location, they are considered as selective carriers for specific effects on oncogenesis (Hong et al., 2014).

Thus, the analysis of reports on the pathogenetic mechanisms of breast tumours in bitches proves their multi-vector character and the need for further, more detailed study of the mechanisms of carcinogenesis in order to improve the diagnosis and identify therapeutic targets to improve the effectiveness of treatment.

Conclusions

The multifactorial etiology and pathogenesis of breast tumours in dogs are shown, the importance of dogs as biological models for the study of this problem in human medicine is proved.

The role of markers of the neoplasia process in most cases is ambiguous in the assessment of their involvement in the mechanisms of tumour aggression and depends on the features of the interaction at the cellular level. The immediate cause of the development of breast tumours in dogs is caused by acute-phase reaction, impaired hormonal and endocrine balance and adverse effects of environmental factors, genomic instability, which leads to disruption of their structure and mutations. The conducted analysis allows us to detail the available information on molecular-biological markers of carcinogenesis, to determine the genetic basis of a complex cascade of initiation of oncogenesis, the development and progression of breast tumours in dogs, allows us to improve the diagnostic criteria and outline the main therapeutic and preventive strategies for this disease, relevant both in human and veterinary medicine.

The prospect of further research is based on the possibility of influencing certain biological targets, which will ensure the high efficiency of destruction of neoplasia cells and inhibit their dissemination against the background of reducing, first of all, toxic effects on tissues and major systems of the patient's body.

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