Molecular biology of cancer: similarities between humans and animals

RESEARCH ARTICLE

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ABSTRACT. Introduction: Cancer is a very important disease especially in older dogs and cats, affecting all breeds with high levels of mortality. In addition, the study of cancer in domestic animals allows progress in the knowledge of human cancer, because they have similarities in several aspects. The most important are related to the clinical part, drug resistance and risk factors for its development. This will expand knowledge in cancer biology, improve palliative treatments and improve the effectiveness of healing attempts. To achieve this, those that resemble the phenotype and molecular aspects should be used, but additionally be identical in the growth pattern, location and immune status of the individual. In this sense it is important both the emulation of genetic alterations, clinical characteristics and variations of the disease due to the biological diversity of cancer. **Aims:** To analyze the participation of the C-MYC oncogene during cancer, and of the genes P53, MDR-1 and Ki-67 as factors for the development of human cancer and its similarities with Canine Transmissible Venereal Tumor (TVTc).**Methods:** Theoretical review of 52 bibliographic sources of the search engines Pubmed, Scopus and Google scholar was carried out. **Results:** Mammalian tumors are the result of alterations in cell proliferation and differentiation genes, inhibition of tumor suppressors, repair gene failures, apoptosis and methylation mechanisms. The protooncogen C-MYC, promotes cell growth and immediate early response, but its expression is well controlled by a series of regulatory mechanisms. It is expressed in different tissues, altering cell differentiation and immortalization and expressing itself in those of greater proliferation. In addition, it is the target of estrogenic action in hormonal receptors due to sensitivity to these hormones during the cell cycle. There are molecular aspects of the C-MYC gene that indicate how it acts during Canine Transmissible Venereal Tumor (TVTc). In the DNA of mammals there are the LINEs that are inserted into the C-MYC gene, causing normal cells to become neoplastic. Canine Transmissible Venereal Tumor (TVTc) is a contagious neoplasm of dogs with two forms, genital and extra genital. The susceptible individual differs from the immune one by its inherent ability to resist contagion, so it is necessary to understand how the immune system is acting and its impact on the final outcome of patients with TVTc. In order for a tumor to become transmissible, cells must undergo adaptive processes to

colonize the host. Inactivity of the p16 tumor suppressor gene is associated with human cancers and is a step for tumorigenesis and disruption of the regulation of this gene leads to a malignant transformation. Resistances may be inherent in the tumor strain itself and may appear during illness. When prolonged application of a drug induces overexpression of P-glycoprotein, cross-resistance with other unrelated drugs often appears, making the cell multidrug. The Ki-67 protein is present during all active phases of the cell cycle, but is absent in stationary cells, therefore, its role as a proliferation antigen is virtually restricted. Increased tissue expression and the correlation between the C-MYC, P53, P21 and P27 proteins indicate reduction and / or loss of their functionality in the micro-environment of the TVTc, whereby apoptotic suppression, maintenance of cell growth and progression is generated of the neoplasm. The gene sequencing technique has allowed us to discover the clonal origin of the specific cell lineage of the TVTc and expand the existing knowledge about neoplasms. **Conclusions:** The ability to determine the presence or absence of genes in the TVTc and its molecular expression, increases both the opportunity to understand the biology of cancer, and to understand from the relationship between the neoplasms of the different species to the common mechanisms between them to develop a competent response from the immune system. This response should be able to control cell proliferation. With this knowledge, better strategies can be proposed to avoid resistance to chemotherapeutics and control the exposure of species to extrinsic factors that influence the presentation of cancer, especially in humans and pets.

Key Words: Canine Transmissible Venereal Tumor, Cancer, suppressor gene, apoptosis, cell cycle, Polymerase Chain Reaction.

Biología molecular del cáncer: similitudes entre humanos y animales

RESUMEN. Introducción: El cáncer es una enfermedad muy importante especialmente en los perros y gatos más ancianos, afectando a todas las razas con elevados niveles de mortalidad. Además, el estudio de las neoplasias en los animales domésticos permite el avanzar en el conocimiento del cáncer humano, debido que tienen semejanzas en varios aspectos. Las más importantes se relacionan con la parte clínica, resistencia medicamentos y los factores de riesgo para su desarrollo. Al utilizar estos factores se busca ampliar los conocimientos en la biología del cáncer, mejorar los tratamientos paliativos e incrementar la eficacia de los intentos de curación. Para lograrlo, se deben usar los factores que se asemejen en el fenotipo y aspectos moleculares, pero adicionalmente ser idénticos en el patrón de crecimiento, ubicación y estatus inmune del individuo. En este sentido es importante tanto la emulación de las alteraciones genéticas, características clínicas y las variaciones de la enfermedad debido a la diversidad biológica del cáncer. **Objetivos:** Analizar la participación del oncogén C-MYC durante el cáncer, y de los genes P53, MDR-1 y Ki-67 como factores para el desarrollo del cáncer humano y sus similitudes con el Tumor Venéreo Transmisible Canino (TVTc). **Metodología:** Se realizó revisión teórica de 52 fuentes bibliográficas de los buscadores Pubmed, Scopus y Google scholar. **Resultados:** Los tumores de los mamíferos son el resultado de alteraciones en genes de proliferación y diferenciación celular, inhibición de los supresores de tumor, fallas en genes de reparación, apoptosis y mecanismos de metilación. El protooncogen C-MYC, promueve el crecimiento celular y la respuesta temprana inmediata, pero su expresión está bien controlada por una serie de mecanismos reguladores. Se

expresa en diferentes tejidos, alterando la diferenciación e inmortalización celular y expresándose en las de mayor proliferación. Además, es blanco de la acción estrogénica en los receptores hormonales por sensibilidad a estas hormonas durante el ciclo celular. Hay aspectos moleculares del gen C-MYC que indican como actúa durante el Tumor Venéreo Transmisible Canino (TVTc). En el ADN de los mamíferos existen los LINEs que se insertan en la el gen C-MYC, haciendo que las células normales se conviertan en neoplásicas. El Tumor Venéreo Transmisible Canino (TVTc) es una neoplasia contagiosa de los perros con dos formas, la genital y la extra genital. El individuo susceptible se diferencia del inmune por su capacidad inherente a resistir el contagio, por lo cual es necesario entender cómo es la acción del sistema inmune y su impacto en el desenlace final de los pacientes con TVTc. Para que un tumor pueda volverse transmisible, las células deberán someterse a procesos adaptativos para colonizar el huésped. La inactividad del gen supresor de tumores p16 se asocia con cánceres humanos y es un paso para la tumorogénesis y la interrupción de la regulación del este gen conduce a una transformación maligna. Las resistencias pueden ser inherentes a la propia estirpe tumoral y pueden aparecer durante la enfermedad. Cuando la aplicación prolongada de un fármaco induce la sobreexpresión de la glicoproteína-P, frecuentemente aparecen resistencias cruzadas con otros fármacos no relacionados, convirtiendo a la célula en multirresistente. La proteína Ki-67 está presente durante todas las fases activas del ciclo celular, pero está ausente en células estacionarias por lo cual, se encuentra virtualmente restringido su papel como antígeno de proliferación. La expresión tisular aumentada y la correlación entre las proteínas C-MYC, P53, P21 y P27 indican reducción y/o pérdida de su funcionalidad en el micro entorno del TVTc, por lo cual se genera la supresión apoptótica, mantenimiento del crecimiento celular y progresión de la neoplasia. La técnica de secuenciación génica ha permitido descubrir el origen clonal del linaje celular específico del TVTc y ampliar el conocimiento existente sobre las neoplasias**. Conclusiones:** La capacidad de determinar la presencia o ausencia de genes en el TVTc y su expresión molecular, incrementa tanto la oportunidad de comprender la biología del cáncer, como de entender desde la relación entre las neoplasias de las diferentes especies hasta los mecanismos comunes entre ellas para desarrollar una respuesta competente por parte del sistema inmune. Esta respuesta debería ser capaz de controlar la proliferación celular. Con este conocimiento se podrán plantear mejores estrategias para evitar las resistencias a los quimioterapéuticos y controlar la exposición de las especies a los factores extrínsecos que influyen en la presentación del cáncer especialmente en los seres humanos y las mascotas.

Palabras Clave: Tumor venéreo transmisible canino, cáncer, gen supresor, apoptosis, ciclo celular, reacción en cadena de la polimerasa.

Introduction

Cancer is an extremely important disease in mammals, particularly canines and felines, and its presentation increases with age in these species.[1] Moreover, it is a condition that is associated with higher mortality levels, regardless of the breed variations that exist in each country.[2] Furthermore, the study of volume increases that spontaneously occur in domestic

animals provides an adequate model for the understanding, diagnosis, and management of cancer in humans.[3] This is because there are similarities between some species regarding important factors such as their location, metastatic pattern, response to treatment, latency, genomic instability, and multifactorial presentation.[4]

Some of the characteristics that have the greatest similarity between humans and domestic animals are related to the clinical development of tumor, development of chemoresistance, and the persistence of a wide diversity of tumor cells in a permissive micro-environment that is under the influence of both genetic and environmental risk factors.[5] In cancer-related studies, it is common to use animal research models to study cancer biology and improve palliative treatments as well as increase the effectiveness of treatment attempts. These models should emulate human tumors in terms of their phenotype and molecular aspects and be identical with respect to important factors such as growth pattern, location, and patient's immune status. Additionally, it is essential to represent genetic alterations and replicate the spectrum of disease and the subtypes of neoplasms that develop in humans because it is necessary to understand the biology of tumors, which is a significant challenge owing to the multiple biological aspects involved in neoplastic development.

The purpose of this documentary review is to analyze the involvement of C-MYC oncogene during cancer development as well as the involvement of genes such as p53, MDR-1, and Ki-67 that are implied in the development of malignant tumors in humans and their similarities with canine transmissible venereal tumors (CTVT).

Cancer mechanisms: In mammals, neoplastic transformation occurs as a result of the accumulation of alterations in essential genes related to cell proliferation and differentiation. The most common gene alterations include a combination of oncogenes, inhibition of tumor suppressor genes, and failures of repair genes, apoptosis, and methylation mechanisms.[6] One of the most disruptive oncogenes is the protooncogene C-MYC belonging to the MYC gene family.

MYC is a family of oncogenes that includes MYCL (L-myc) and MYCN (N-myc). It is involved in several signal transduction pathways that promote cell growth and immediate early response for membrane receptor complexes and their ligands. MYC expression is well-controlled by numerous transcription regulatory mechanisms within its proximal promoter region. In studies performed on chicken tumors, the MYC-C gene that causes sarcomas and leukemia was isolated. Additionally, alterations of this gene have been found in Burkitt's lymphoma, multiple myeloma, human colon carcinoma, T-cell leukemia, and in many other tumors, resulting in a direct association between C-MYC alterations and human cancer. It has also been identified as one of the genes involved in the collective reprogramming that transforms fibroblasts into pluripotent cells.[7] The protooncogene C-MYC is expressed in different tissues, and is involved in the synthesis of transcription factors that bind to DNA and regulate the expression of other genes and the cell cycle.[8] This protooncogene participates in cell apoptosis, proliferation, differentiation, and immortalization and is expressed in cells with the highest proliferation rate, causing alterations in the locus and loss of control of its expression. Moreover, it promotes the passage of the cells from the G0 phase to G1 phase. Throughout the G1 phase, it induces gene transcription and is involved in cell growth and proliferation during apoptosis.[9] There

is a marked C-MYC predominance as a target of estrogenic action in hormonal receptors because half of the genes sensitive to these hormones are also sensitive to C-MYC during the transition from G1 phase to S phase in the cell cycle.[10] Although the genes that are targeted by oncogenes and those which interfere with that interface of the cell cycle are unknown, it has been possible to determine the molecular aspects of the C-MYC gene that allow for the understanding of the possible mechanisms through which the gene acts during the growth of neoplastic cells, including cells of CTVT.

The C-MYC protein has two domains and area region that is rich in glutamine, which is essential for the development of neoplastic activity.[11] The first domain is the C-terminal or helix–loop–helix leucine zipper (HLH/LZ), which provides terminal amino acids necessary for dimerization with the myc-associated factor X protein (MAX), and the specific nucleotide adenosine diphosphate binding sequence (DNA); this dimerization forms a specialized and essential complex for cell activity.[12] MAX protein may act as a cofactor during activation or as a transcription repressor.[13] The second domain is the N-terminal transactivation through interaction with the so-called TATA- box binding protein.[14] It comprises a thymine–adenine tetranucleotide which is the central promoter sequence and the site of transcription-factor binding.[15]

C-MYC LINE Rearrangement: In animals' DNA, there are fragments of repetitive sequences of transposable elements, which include the long interspersed nuclear elements (LINEs). These elements comprise a 5´ regulatory region and two open reading frames (ORF) that are an RNA sequence from an initiation codon and the translation termination codon. They transcribe the entire length of the element into mRNA, translate ORF within the proteins, copy RNA into DNA, and insert this DNA back into the genome.[16] LINEs are characteristic of mammals and are inserted in the 5' region of the first exon of the C-MYC gene, causing it to express its ability to transform normal cells into neoplastic cells, as occurs during the development of CTVT.[17] The DNA of this neoplasm is made up of sequences that overlap with the canine genetic material and cross-hybridize with human genetic material. For its activation, it requires additional factors such as the loss of p53's ability to act as an activator of sequence transcription. This mutant p53 gene can regulate the expression of the endogenous C-MYC gene and act as a promoter.[18]

The presence of LINE in the genome represents a great threat to its integrity; this is owing to their ability to induce DNA damage, insertion mutations, and chromosomal rearrangements. This is particularly critical in germ cells because the changes induced in the genome will be transmitted to the next generation.[19] There are other inheritable changes that are associated with the silencing and overexpression of key genes involved in the regulation of the onset and progression of cell transformation. These genes are not the product of mutations or promoters but of processes such as DNA methylation.[20] It is important to mention that demethylation of the entire genome can be another step in carcinogenesis[21], which is owing to its relationship with the presentation of tumor cells and defects in the said demethylation; it could contribute toward the genomic instability of certain cell lines with the presentation of abnormal chromosomal structures.[22] This indicates that the LINE methylation status reflects the level of methylation throughout the genome, and it is representative of the overall losses of DNA methylation and therefore has

the potential to be used as an important marker in the early surveillance of neoplastic disease.[23]

During the process of obtaining new LINE DNA, reverse transcription is performed with a target primer. It begins with the breaking of a single strand by the nuclease encoded by the element at the integration site, followed by binding to the target site. The intermediate transposition of LINE RNA is activated by polymerase II promoter activity, and the translation is activated by ORF1 and ORF2 proteins that are bound to the original RNA. In general, the new LINE is incomplete owing to the loss of sequence length because reverse transcription ends before completing the first DNA strand, and because it is incomplete, it cannot be transposed. In the case of a mutation that allows for equality in size, it will not be functional owing to the preferential association affinity with its original RNA.[24]

C-MYC LINE rearrangement is important in the study of CTVT molecular biology because, although the latter has been reported to be a spontaneous remission tumor, this mutation may be related to the expression of different genes during neoplastic development. Therefore, it is important to review the most important aspects of genetic expression during cell proliferation, drug resistance, and the activation of suppressor genes that exist in neoplasms. Despite this, some relevant aspects, such as diversity in the affected systems, clinical picture, and CTVT metastatic potential should be considered.

Canine transmissible venereal tumor: CTVT is a contagious round-cell neoplasm that affects dogs of both sexes in tropical and subtropical countries.[25] It is endemic in at least 90 countries, which is owing to factors such as dogs traveling freely; this creates a natural neoplasm reservoir and suggests a homogeneous distribution, regardless of the altitudes and diversified climates. There is a greater predominance in rural areas, particularly in those with a prevailing jungle habitat, coupled with the lack of optimal veterinary services.[26] There are two forms of this tumor: genital and extragenital. The genital form is transmitted through natural mating, whereas extragenital form is transmitted through socialization activities such as sniffing or licking and in some cases, this form metastasizes.[27] The epidemiology of the disease suggests that there is no predilection for sex or breed barriers, and despite infecting foxes, wolves, and coyotes, there is no evidence that indicates it has been transmitted to other species.[28] Therefore, it can be said that CTVT is a frequent neoplasm in places with an overpopulation of stray dogs, which, together with the species' pattern of social behavior, make domestic dogs predisposed to being infected by sharing the same habitat and having potential contact with the neoplastic cells of sick individuals. This could happen because dogs have gregarious habits that induce them to make direct contact with each other and when a healthy dog comes in direct contact with a dog with CTVT, it can easily contract the tumor.

In addition to the genital transmission caused by sex, the tumor can be transmitted when a susceptible or immunocompromised dog licks the genitals of another affected dog and then their own or those of another; this can be defined as a natural allograft. During the last century, studies were conducted in which the passage of the tumor was tracked through 40 generations of dogs of different breeds. It was found that there were no changes in the histopathology of the majority of the tumors during their passage through the generations.[29] Tumor transmission is achieved via the implantation of its viable cells in the

mucous membrane,[30], [31] particularly in abrasions or membranes that have lost their integrity,[32] and it grows progressively for 12 weeks until it becomes vulnerable to the individual's defenses. In 1876, the first experimental transplant of the tumor was performed. Subsequently, in 1898 and 1902, sick animals were studied, and it was found that some individuals were immune, a certain group had spontaneous healing, and others apparently died because they were extremely sensitive or immunocompromised.[33] There are those who attribute a histiocytic origin to the disease because of the evidence of macrophage expression.[34] In accordance with the above, it is clear that the susceptible individual differs from the immune individual owing to its inherent ability to resist infection; therefore, it is necessary to understand how the immune system acts and its impact on the final outcome of patients with CTVT. Therefore, knowledge of the molecular characteristics involved in the development of neoplasm has promoted the development of methodologies to support the diagnosis, particularly in atypical cases.

Regarding the diagnosis, cytology was found to be the method of choice for CTVT because it is quickly and simply performed and is minimally invasive. In general, the specimens obtained show multicellular content, with round or oval units having well-defined edges, a round or oval nucleus, often eccentric, of variable size, thick chromatin, and one or two nuclei. Cytomorphological differentiation is performed by observing cytoplasmic vacuoles and through analysis of aspects such as size, cell shape, and cytoplasm–nucleus relationship. According to the findings, CTVT can be classified into lymphocytoid, plasmocytoid, and mixed type.[35]

CTVT biology: During the course of the disease, the C-MYC oncogene is reorganized in the genetic material of the neoplastic cell through the insertion of LINE at the 5' position with respect to the first exon of C-MYC.[36]

The rearranged genes are identical, and the genome integration is performed in exactly the same C-MYC nucleotide.[37] The presence of this LINE element near C-MYC (LINE/C-MYC) has been used as a diagnostic tool for a definitive diagnosis in cases of CTVT using the polymerase chain reaction in situ (PCR) and conventional C-MYC PCR LINE in controversial cases. Conventional histological and cytological analyses should be performed together with the LINE/C-MYC PCR analysis to improve diagnostic accuracy.[38] This is because the development of CTVT neoplastic cells occurs in a unique manner as it follows a predictable growth pattern with a progressive growth phase, a static phase, and a regression phase, which are followed by immunity to transplantation in immunocompetent adults, and metastases are observed in puppies and immunosuppressed dogs.[39] Immune evasion of a tumor and failure of defenses against tumorigenesis indicate malignancy. It also implies that the immune system ignores and/or loses its ability to react against the formation of tumors; thus, when immunity is defective, neoplasms increase.[40]
It should be considered that for a tumor to become transmissible, neoplastic cells must first undergo different adaptive processes and thus survive host colonization. After inoculation, the tumor genome is reconfigured by millions of mutations and thousands of structural rearrangements, changes in the number of copies, and insertions of retrotransposons. These are coded in the same manner in dogs worldwide by the activation of DNA repair mechanisms, and the protection against additional mutation and instability obtained by compensating telomeres, which protect the genome.[41] Thus, CTVT can interact accordingly

with its environment and subsist on it. This is because, for several millennia, its cell has had a parasitic neoplastic form and had the ability to keep its genetic code intact.[42] C-MYC oncogenes can induce more subtle alterations in growth, such as senescence retrieval or immortalization. Despite this, some evidence suggests that it takes several stages to generate totally malignant cells.[43]

In accordance with the above, tumor suppressor genes are highly important because when they lose their activity, they also lose their ability to respond to the control mechanisms that regulate cell division, thereby causing an uncontrolled proliferation which leads to the worsening of the disease.[44] Inactivity of the p16 tumor suppressor gene is associated with human cancers and is a step in tumorigenesis, whereby disruption of p16 regulation can lead to aberrant cell proliferation, resulting in malignant transformation.[45] These transformations sometimes acquire characteristics that cause chemotherapeutics to lose effectiveness.

MDR-1 gene: MDR-1 is related to resistance, which is known to be inherent to the tumor strain itself and can express during disease manifestation owing to cell mutations, genetic instabilities caused by drugs used, which can induce natural selection, and the overgrowth of resistant clones.[46] When prolonged application of a drug induces P-glycoprotein overexpression, cross-resistance with other unrelated drugs frequently occurs, making the cell multidrug resistant.[47] Further knowledge regarding the genes present in the ABCB1 amplicon and its role in cancer and chemoresistance may facilitate the identification of new markers and provide important information on tumorigenesis and the mechanisms of multidrug resistance (MDR). A possible strategy to overcome MDR in cancer is to consider the orientation of proteins which are often overexpressed along with ABCB1 in MDR tumors and be used as biomarkers of poor results in patients with cancer.[48]

Ki-67 and other proteins: Ki-67 protein is present in all active phases of the cell cycle (G1, S, G2, and mitosis); however, it is absent in the resting or stationary cells, owing to which it is virtually restricted in its role as a proliferation antigen. This makes the corresponding gene a more specific determinant of cell multiplication in neoplasms.[49] Despite this, increased tissue expression and the correlation among C-MYC, p53, p21, and p27 proteins indicate a reduction and/or loss of its functionality in the CTVT micro-environment, with consequent apoptotic suppression, cell growth maintenance, and neoplasm progression.[50]

Molecular diagnostic techniques: It is clear that, although it is not yet possible to explain individuals' susceptibility to developing cancer, the technique of gene sequencing has allowed us to discover the clonal origin of the specific cell lineage of CTVT and expand the existing knowledge regarding neoplasms.[51]

It is possible to detect CTVT in specimens with very little genetic material; even 10 ng of DNA be amplified to produce amplicons of 550 bp to reach a diagnosis. Therefore, when analyzing canine tissues and in the absence of neoplastic cells, PCR result will be negative.[52] Furthermore, it is known that the insertion of the LINE element in the C-MYC gene is characteristic of a specific molecular change in CTVT,53 which is important because the evaluation of this molecular rearrangement is useful for a complementary diagnosis in cases of undifferentiated CTVT.

Conclusion

By taking advantage of the ability to determine the presence or absence of genes in CTVT and their molecular expression, it is possible to provide elements that will, in the future, allow the determination of the biological mechanisms underlying the development of cancer, including understanding the relationship between neoplasms of different species and the common mechanisms among them to develop a competent immune response, which can control cell proliferation in cancer as it happens in CTVT. This will encourage the development of better strategies to prevent the development of resistance to chemotherapeutics and to control the extrinsic factors that influence the presentation of cancer, particularly in humans and pets.

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