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The Critical Role of TP53 in Developing Leukaemia in Human and Dogs, Review Article

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ABSTRACT

Haematological cancer is an important disease and often diagnosed in both humans and dogs. In recent years, there is an increase in the incidence of cancer, in particular leukaemia, due to different causes. This remarkable increase of diagnosed cancer cases may indicate a very dangerous health issue. The main causes of developing such cancer are due to genetic aberration and chromosomal rearrangements. These alterations may appear as mutations that affect a wide range of genes. One of these frequently mutated genes is TP53. The TP53 gene plays a central role in controlling critical functions inside the cell, such as the cell cycle, cell metabolism, DNA repair process, and serves as a transcriptional factor for a vast number of genes. The mutations in the TP53 gene are resulting in the development of various spontaneous types of cancer in both humans and dogs, including haematological cancer. The research that is interested in haematological cancer in veterinary aspects is limited. Therefore, the main focus of this review is to highlight the relationship of developing haematological cancer in both humans and dogs and the role of TP53 mutations.

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INTRODUCTION

Haematological malignancies are frequently diagnosed in mammalian kingdom species, especially humans and dogs. These types of cancer arise as a result of animal immunodeficiency with specific genetic aberration features and similar mechanisms of development to what has been observed in humans [1-3].

The physiological similarities between humans and dogs introduced this animal (Dog) as a biomedical model for studying carcinogenesis and novel therapies for such types of cancer compared with the rodent model [3]. Several causes have been identified to explain this preference according to the following: 1. Both humans and the companion dogs are living in the same environment. 2. Canine cancers occur spontaneously, while in lab animals, cancer mostly is induced as a result of genetic manipulation and/or exposure to the carcinogenic agents. 3. A variety of canine and human tumours have similar tissue origin, including lung cancer, melanoma, osteosarcoma, mammary carcinoma and head and neck carcinoma, as well as the response to the anti-cancer agents [4,5].

The haematological cancers are a heterogenous condition which includes a range of haematological tissue illnesses, such as leukaemia and lymphoma [6,7]. Leukaemia's are types of disorders which are recurrently diagnosed in humans and dogs and include acute lymphoblastic leukaemia (ALL), chronic lymphoblastic leukaemia (CLL), acute myeloid leukaemia and chronic myelogenous leukaemia (Fig. 1). Such illnesses may impact different age sectors, such as children, young adults, and the elderly, with incidence rising with age [8].

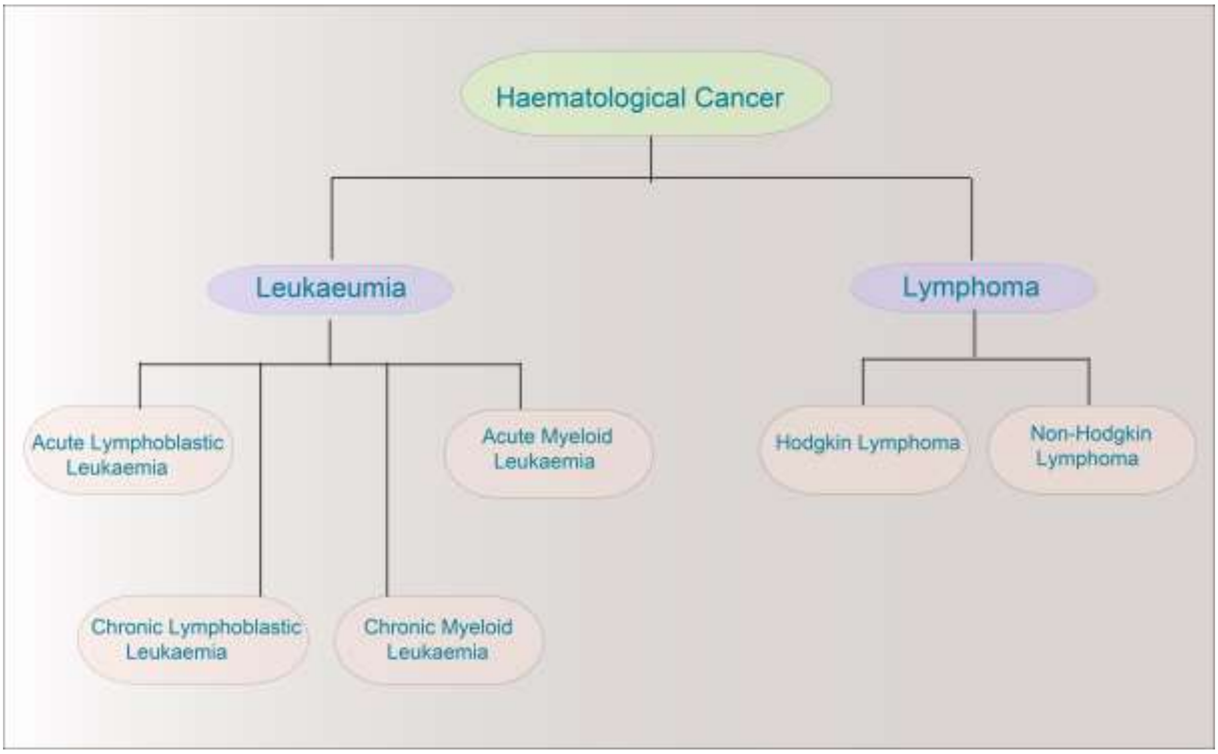

Fig. 1. A schematic illustration showing the general classification of haematological cancer.

Collectively, from 1990 to 2018, the observation indicated a significant increase in leukaemia cases from 297,000 to 437,033. It was reported by the Global Cancer Observatory in 2018 that leukaemia was the 13th most predominant cancer in humans globally, although the prevalence of leukaemia has risen over time. While in 2020 the prevalence of this illness and mortality rate were increased about 2.5% and 3.1% respectively [9,10]. Other observations suggested that the predictable crude incidence in the Middle East and Northern Africa (MENA) region is 4.0 per one hundred thousand for females and 5.3 per one hundred thousand for males [11]. Moreover, in the same context, a report study carried out by the Gulf Cooperation Council showed a sharp rise in leukaemia cases, which is considered the fourth most dominant malignancy among other types of cancers in the Arabic Gulf region [12].

Cancer is considered one of the most common causes that increases mortality in dogs, affecting roughly four million dogs per year [13]. The incidence estimation indicated that around twenty-five per one hundred thousand dogs annually are affected with haematological cancer. Primarily, the clinical observation revealed that the affected dogs were aged between middle-age and older age [14]. In the case of leukaemia, the true occurrence in dogs is still unknown so far. However, two retrospective studies referred to lymphocytic leukaemia being more frequently diagnosed compared with the other types of leukaemia’s, namely myelogenous, which are rarely observed in dogs [15,16]. The metadata from different countries, such as Canada, the United States, the United Kingdom, and the Netherlands have indicated that the risk of the development of haemopoietic cancer is specifically correlated with dog breeds. This suggests that a genetic factor is playing critical role for disease-associated specific breeds, such as Bullmastiff, Rottweiler and Scottish Terrier lines [17].

GENERAL CLASSIFICATION OF LEUKAEMIA

Acute Lymphocytic Leukaemia (ALL)

Basically, ALL is a haematologic neoplasm of T or B lymphoblasts distinguished by continuous abnormal proliferation of immature lymphocytes and their ancestors. Which, finally, this condition resulting in the replacement of the elements of bone marrow and the other lymphoid tissue organs is considered a typical illness pattern of ALL [18]. Frequently, the recorded clinical observations are summarised as follows: anaemia, neutropenia and thrombocytopenia. In addition, the other specific related symptoms include fatigue, spontaneous bleeding, recurrent infections due to immune depression, as well as weight loss, night sweats and fever. Moreover, lymphadenopathy, splenomegaly and hepatomegaly can be diagnosed in up to half of patients. It has been found that the central nervous system may be affected by an increase intracranial pressure due to the symptoms of cranial neuropathies [19].

The main aetiology of ALL is unknown, but environmental factor and diet may play a crucial role in such illness. Studies have indicated that the genomic alterations enhance ALL development; in particular, TP53 (Tumour protein 53) mutations can be strongly associated with ALL initiation and progression [18,20,21]. DNA damage is thought to be the key initiator of such disease, resulting in lymphoid cells undergoing uncontrolled proliferation and spread throughout the patient’s body [22].

Chronic lymphocytic leukaemia (CLL)

Chronic lymphocytic leukaemia, a haematological aberration, is characterised by the proliferation of neoplastic small, mature dysfunctional lymphocytes with increased peripheral lymphocytosis, originating from B lymphocytes. CLL is affecting dogs with ages varying from middle aged to geriatric [23, 24]. Similar to ALL, the precise cause of CLL is still unknown. However, a collection of different causes may control the development of CLL. The genetic factor is more dominant than the environmental factor. Roughly 15-20% of CLL patients have a CLL family history or may have a lymphoproliferative disorder [25]. The variation in DNA sequences level related to critical genes such as FBXW7 (F-box and WD repeat domain containing 7), TP53 (Tumour protein 53) and NOTCH (Neurogenic locus notch homolog protein 1). These genes are considered predisposing factors to the development of CLL, as well as chromosomal aberrations and the number of copy variants of microRNA, such as miR15A and miR16-1 deletions [26,27]. It has been found that exposure to some chemical carcinogenic compounds, the uranium ionizing radiation and non-ionizing radiation may increase the risk of CLL incidence [27].

At the molecular level, CLL initiation and progression is motivated by impaired programmed cell death and enhanced uncontrolled cell proliferation accompanied by aberrant cellular signalling pathways and genetic abnormalities, especially mutations in TP53 [28]. It has been recorded that one in four chromosomal rearrangements occur in around 80% of CLL cases. These abnormalities are related to B cells, which include del 17p12, del 11q22-23, Trisomy 12 and del 13q14 [29]. Importantly, understanding this chromosomal abnormality is vital to determine the precise treatment regime [30].

Acute myeloid leukaemia (AML)

Acute myeloid leukaemia is a myeloid neoplasm initiated from primitive hematopoietic cells known as blast that proliferate rapidly in the bone marrow. Such abnormal proliferation results in rapid bone marrow failure due to an increase in the ineffective erythropoiesis and the megakaryopoiesis. Clinically, this condition is illustrated through the decreased red blood cells and platelets production [31]. In humans, the annual incidence of AML cases indicated that there were around twenty thousand cases per year, which means about 4.3/100,000 of the population in the United States alone. Moreover, the median age among the diagnosed cases is about 68 with, a higher incidence recorded in males compared with females [32].

According to the AML heterogenicity, this disease can be categorised into three groups, namely mild, intermediate or high risk based on the molecular and cytogenetic characterisation [33]. The main genetic aberrations that accompanied AML include chromosomal translocation inv (16) (p13.1q22) or t (8;21) (q22; q22.1) [34]. It has been found that mutation in the NPM1 (Nucleophosmin 1 encoding gene) is the most frequently observed in AML [35]. In case of intermediate risk, the recorded mutation known as FLT3-ITD (FMS-like tyrosine kinase-3 internal tandem duplication) or t (9;11) (p21.3; q23.3) or the rearrangement following the MLL: KT2A mutation (Mixed lineage leukaemia: Histone-lysine N-methyltransferase 2A). Finally, in the case of the high-risk AML, several molecular abnormalities were recorded, such as monosomy 5/deletion 5q or 7/deletion 7q. In addition, other complex karyotype mutations, namely TP53 (tumour protein 53), SRSF2 (Serine/arginine-rich splicing factor 2), EZH2 (Enhancer of zeste homolog 2), ASXL (Additional sex combs-like protein 1) or IDH (Isocitrate dehydrogenase 1 or 2) [36, 37]. Importantly, TP53 mutations are correlated with resistance to chemotherapy and poor prognosis [36].

Chronic Myeloid leukaemia (CML)

Chronic myeloid leukaemia is a form of leukaemia that is initiated from hemopoietic tissues (bone marrow) and characterised by abnormal proliferation of myeloid tissue. This type of leukaemia is identified by translocation of t(9;22) (q34;q11), termed the Philadelphia chromosome, resulting in the fusion of genes, namely BCR (Break point cluster region) and ABL1 (proto-oncogene 1, non-receptor tyrosine kinase), leading to the formation of the fused pathogenic oncogenes BCR-ABL, which subsequently affects the downstream pathways, including activation of the Tyrosine Kinase pathway [37]. The activation of this pathway results in the increased proliferation of mutant hematopoietic stem cells compared with the normal cells, leading to gradual accumulation and displacement of the abnormal HSCs [38]. Therefore, the presence of the BCR-ABL1 fusion determines the pathophysiology of CML. However, the mechanism of Ph chromosome formation and the time of clinical symptoms appearance is still unknown [39]. Previously, the Ph chromosome was believed to have been initiated as a result of the influence of radiation, according to some observations in Hiroshima and Nagasaki following the atomic bomb [40]. Some in vitro studies have revealed that the expression level of BCR-ABL1 correlates with the exposure to high doses of radiation in some myeloid cell lines [41]. However, the Ph chromosome can be initiated spontaneously as a result of random translocation. CML has three different phases, namely the chronic phase, the accelerated phase and the blast phase. The clinical signs of CML ranged from asymptomatic to obvious leukostasis, according to the stage of the disorder. The leukostasis frequently occurs in the blast phase. The blast phase in the case of CML is similar to AML and ALL [37].

THE IMPORTANCE OF TUMOUR PROTEIN 53 (TP53) FUNCTION AND STRUCTURE

Carcinogenesis has been defined as a process by which a normal cell is transformed to malignant through multiple steps. Consequently, this process is leading to numerous genetic changes allied with the effect of precise one or multiple genotoxic factors. One of these alterations is the TP53 a tumour suppressor gene mutation [42, 43]. This gene is mutated frequently in haematological cancers. These mutations are also associated with resistance to different chemotherapeutic regimes leading to poor patient's outcomes [37].

The first known description of p53 was in 1979 as a cellular factor interacting with the Simian Vacuolating Virus 40 tumour antigen to form a complex [44, 45]. In the same context, several studies have revealed that p53 accumulated excessively in both cancer cells negative for viral infections and the cells expressing viral tumour antigen, while in normal and uninfected cells, the p53 level was low [45,46]. Therefore, it has been considered an oncogene due to cDNA clones' mutation, which induces cell transformation. Eventually, according to an invitro study the wild type TP53 was classified as a tumour suppressor gene by detecting the inhibition of oncogenesis [48].

The TP53 gene is located on chromosome 17 at p13.1 in humans, while in dogs, it is located in chromosome 5. According to the National Centre for Biotechnology Information (NCBI) database, the human TP53 gene shares around 87% DNA sequence similarity with that of the canine TP53 gene. It has been found that canine TP53 is mutated in a variety of dog cancers.

In terms of protein structure, the TP53 gene encodes the p53 protein, which consist of 393 amino acids in humans. While the canine p53 consists of 381 amino acids and shares 81% identity with the human one. The difference can be explained due to 13 extra amino acids located on the human exon four [49, 50]. The p53 protein has many functions summarised as a tetrameric transcription factor that controls the regulation of the different pathways by controlling the expression of a vast set of genes, around 200 genes, which in turn translates to different proteins involved in the response to cellular stress, such as DNA repair, metabolism, cell cycle arrest, apoptosis and other tumour suppression mechanisms [48, 49].

Numerous cellular stresses, such as hypoxia, DNA damage, oncogene expression and replicative stress, can activate TP53. Primarily, the TP53 transcriptional factor regulates many transcriptional processes according to the cell and cellular stress type. For instance, in normal cases, DNA damage may cause cell cycle arrest, which in a way activates DNA repair mechanisms and cell survival or apoptosis pathways [51]. However, in many cancers, TP53 mutation may lead to direct inactivation of p53. Mostly, this gene is the most common mutated gene in various human cancers, namely breast, colon, lung, brain, stomach, pancreas, bladder and leukaemia. The mutation targeted the DNA-binding domain region, resulting in changing the amino acid sequences in the p53 protein [49, 52, 53].

The p53 function is comprehensively related to the molecular structure of this protein [54, 55]. The p53 protein structure comprises the N-terminus, which has two domains, namely the TAD (transcriptional-activation domains) and the PRD (Proline rich domain), followed by an important domain called the DBD (DNA binding domain), while at the C-terminus, two domains were characterised, the TD (Tetramerization domain) and the RD (Regulatory domain) (Fig 2) [56]. The regions forming p53 protein are intrinsically tend to be disordered, especially, TAD, CTD, as well as the linker between DBD and TET. Such disordered regions give the permission to interact with other proteins as partners to facilitate the precise function. The complex structure of the p53 determines the unique characterisation and the contribution in a wide range of functions [55].

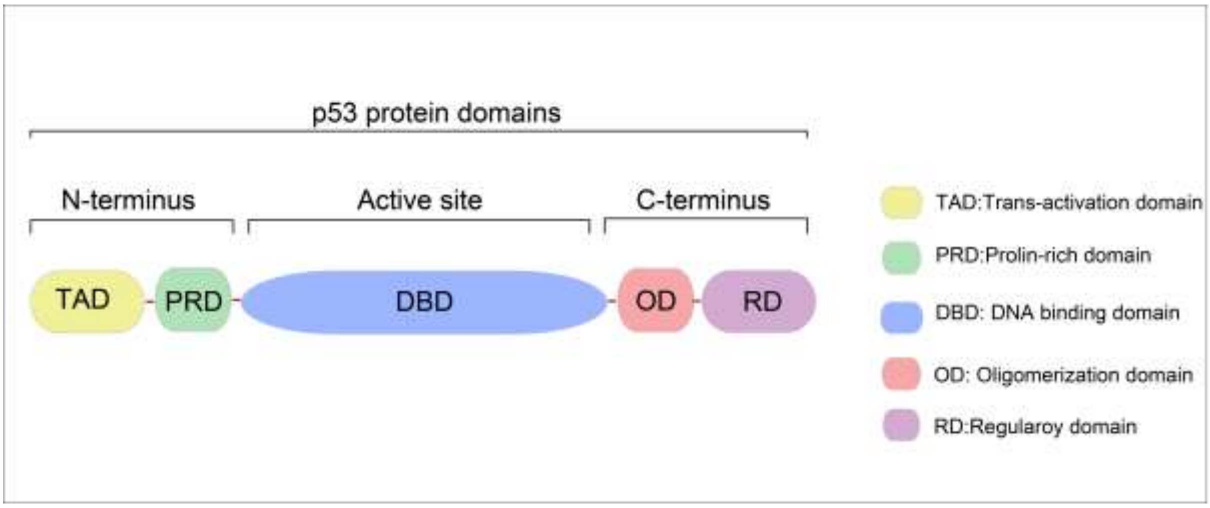

Fig. 2. A schematic illustration showing p53 protein structure.

THE MUTATION TYPES OF TP53 AND THEIR IMPACT ON TRANSLATION P53 PROTEIN

The TP53 gene composition consists of eleven exons. The sequence of this gene exhibited a high degree of similarity across mammalian kingdom species, in particular dogs [56]. It has been observed that many dog-human homologies, including TP53, mutated at the pathway level in different cancers, especially leukemic types. Most of these mutations have a strong correlation with tumour gene mutation burden, and this observation supports the dog-human correlation [57].

The most common mutations of TP53 in different cancers are missense single base pairs located at exons 4-8, which form the DNA binding domain [20]. Similar to human tumours, in dogs TP53 mutations have been identified in a variety of tumours, such as lymphoma, mammary carcinoma, osteosarcoma, papilloma, thyroid carcinoma and other soft tissue sarcomas [58, 59].

There are six frequently noticed mutations in the DNA binding domain, are G245S, R175H, R249S, R273H/S, R248Q/W, and R282W. These six mutations known as six hotspot mutations. In spite of the importance of these mutations, however, they cover only one quarter of TP53 all mutations which are recorded in different cancers. As a result of these missense mutations, the sequence of the amino acids would be changed, leading to the loss the ability of DNA binding activity and, in turn, loss of function of TP53 [49, 60]. TP53 mutants that mediated cancer development have the ability to revoke the wild type TP53 indicated transactivation, which is known as dominant negative potential. Both wild type TP53 dimer and the TP53 mutant dimer are forming the p53 hetero-tetramer. The tumour cells are sheltering the heterozygotes of wild type TP53 and TP53 mutation [61]. Surprisingly, some of the TP53 loss of function mutations have gain function activity (called insertion mutation), and this has been approved in several animal model studies [20]. While some of the TP53 mutations display various transactivate activities. One of these mutations, p.S121F, can transactive some target genes such as TNFRSF10B, BBC3 and BAX then trigger apoptosis, however, cannot induce expression of the CDKN1A gene [43,49,57, 62]. On the other hand, some other mutations, such as R282W, indicated partial p53 activity with or without sensitizing to heat. Whereas other alterations, including R337H, illustrated similar activity of the wild type or increased transactivating activity [42, 63].

CONCLUSION

To summarize the main points that are illustrated in this review, the canine model is considered one of the models that are used to study human cancers due to many causes. One of these quietly important causes is the genetic similarities. At the molecular level, the TP53 gene has a similar structure in both humans and dogs, and the alteration in this gene would affect a wide variety of cell functions, especially cell cycle. The most important mutations that occur in the DNA binding domain which are responsible for developing different cancers, in particular leukaemia.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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