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MOLECULAR, MORPHOLOGICAL AND CLINICAL CHARACTERISTICS OF SPONTANEOUS CANINE COLORECTAL CANCER – A REVIEW

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ABSTRACT

Cross-species comparison analysis studies are of immense importance in veterinary and human oncological research. Of the various non-rodent species available, dogs have gained most attention as potential animal models for the study of colorectal cancer. Domestic dogs developed evolutionally through a mutually beneficial relationship with humans. Because dogs share the same environment as humans, they are exposed to the same potentially harmful substances which may act as carcinogens in both species. Intestinal adenocarcinomas in dogs are naturally occurring heterogeneous tumours, which have the characteristics of sporadic human malignancies and therefore are more suitable for detailed oncological study than most xenograft or genetically modified rodent models. Furthermore, the canine genome has been comprehensively analysed and sequenced to a 7.6-fold coverage, and a very accurate version of this sequencing is available for study. The purpose of this manuscript is to present a comprehensive review of published data related to colorectal cancer in dogs. In addition, data regarding interspecies comparison of molecular events driving canine and human intestinal carcinogenesis is presented.

Key words: canine adenoma; canine adenocarcinoma; canine animal models; canine colorectal cancer

INTRODUCTION

Colorectal cancer is a heterogeneous epithelial malignancy with many histological subtypes, variable clinical presentation, and a poor prognosis in many patients [33]. At the time when the diagnosis of colorectal cancer is made, approximately 25 % of patients have locally advanced disease and 20 % present with distant metastasis [3]. Because of this, there is an urgent need to conduct detailed research studies, which hopefully will lead to improvement of our ability to prevent, diagnose, and treat this disease. To identify causal genetic alterations driving carcinogenesis, the development of cross-species comparison analysis studies is of immense importance [18]. Of

the various non-rodent species available, dogs have gained most attention as potential animal models for the study of colorectal cancer [40]. The purpose of this manuscript is to present a comprehensive review of published data related to the topic of colonic and rectal adenocarcinomas in dogs. Additionally, we also focus on an interspecies comparison of molecular events driving canine and human intestinal carcinogenesis.

MATERIALS AND METHODS

Dogs as potential animal models for oncological research

Companion animals like the dog potentially are valuable models for the study of human cancer for several reasons: firstly, domestic dogs developed evolutionally through a mutually beneficial relationship with humans, which started at least 15000 years ago and may go back as far as 100,000 years [32, 36]. Because they share the same environment as humans, they are exposed to potentially harmful substances and dietary factors which may act as carcinogens in both species [2, 29, 37]. Indeed, known risk factors for the development of cancer in dogs include obesity as well as other inappropriate quantitative and qualitative dietary factors, exposure to ionizing radiation, environmental air pollutants and other substances which are also known to be involved m in the process of carcinogenesis [23, 40]. Secondly, colorectal carcinomas in dogs are naturally occurring heterogeneous cancers which share the characteristics of sporadic human malignancies and therefore fit better for the purpose of efficient oncological study than most xenografts and genetically modified rodent models [34].

Over the past several years, progress in molecular genetics and other basic sciences has been able to provide valuable scientific data which may be used to improve oncological research [18]. The genome of the dog has been comprehensively analysed and sequenced to a 7.6-fold coverage, and a very accurate version of this sequencing is available for study [23]. This differs from other analysed mammals like, for example, cats in which only a 2.8-fold coverage of the genome is available [27]. Conducting comprehensive oncological research based on bioinformatical analysis is, therefore, more readily carried out in dogs than cats [23]. Furthermore, when compared with humans, the genome of dogs undergoes wide-spread genomic rearrangement [16, 23]. Because of these advantages, the study of sporadic canine colorectal adenocarcinoma is extremely valuable when studying the basic and clinical aspects of the corresponding tumours of humans [18, 29].

Epidemiology, anatomical localization, and morphology of canine colorectal tumours

Compared to humans, canine gastrointestinal tract neoplasms are less often encountered, accounting for 3 % to 10 % of all tumours in this species [8, 14]. However, in dogs, the alimentary tract tumours are more prevalent compared with the sporadic gastrointestinal tumours occurring in cats or other mammals, underscoring the value of dogs as comparative animal model for human oncological studies [18, 25].

The alimentary tract tumours are more prevalent in some canine breeds than in others [11, 31]. For example, a study conducted by Saito and colleagues demonstrated that gastrointestinal tract tumours develop significantly more commonly in Jack Russell terriers and Miniature Dachshunds compared with other dog breeds [31]. Miniature Dachshunds are reported to be predisposed to the development of inflammatory polyps in the large intestine, and these may progress to adenomas and eventually adenocarcinomas [30].

In general, although tumours of the digestive system can develop throughout the gastrointestinal tract of dogs, both benign and malignant neoplasms are found significantly more often in the large intestine [8] with up to 60 % affecting the large intestine [7]. Of these, 50 % to 60 % are malignant [1]. Histogenetically, most malignant tumours are of epithelial origin, with adenocarcinoma being the most common histological diagnosis [25]. Other less commonly encountered large intestine malignancies include: lymphomas, haemangiosarcomas, leiomyosarcomas and plasma cell neoplasms [9, 21].

Regarding more specific localizations of intestinal malignancies within the colon of dogs, adenocarcinomas have a significant predilection for the distal part of the descending colon and the rectal area [35]. Similarly, benign lesions such as adenomatous polyps are also more often encountered in the distal colonic area and rectum [14, 35]. These polyps are the most common benign tumours in the region of the gut [1]. Other less commonly encountered benign tumours are colonic leiomyomas and fibro-

mas [25]. Similarly, as in humans, adenomas localized in the sigmoid and descending colon and the rectum usually morphologically manifest as pedunculated polyps [8]. In the minority of cases which are present in the transverse or ascending colon, adenomatous polyps usually exhibit a sessile and annular appearance and may be the cause of strictures with narrowing of the luminal space [35].

Molecular pathogenesis in canine colorectal adenocarcinoma

One of the reasons why dogs gained attention as potential animal models for the study of colorectal cancer are the interspecies similarities in activated oncological pathways leading to the development of intestinal adenocarcinoma [17, 18].

T a n g et al. [34] analysed copy number abnormalities and other genetic alterations in canine colorectal carcinomas. Studying of 10 spontaneously occurring tumours in dogs showed a high degree of genetic homology between sporadic canine and human tumours. T a n g et al. [34] in their study, also demonstrated amplification of 5 % to 22 % of the canine genome in the analysed adenocarcinoma samples. As is the case in humans, they showed that the total number of altered genetic sequences directly correlated with the stage of progression of the oncological disease, and with the microsatellite instability status. When mapping genetic alterations in dogs, they noted that the analysed mutated canine genes which caused activation of signalling pathways leading to the development of colorectal cancer in dogs, are analogous to oncological pathways implicated in the formation of human intestinal adenocarcinomas. Overall, a significant overlap of copy number alterations was demonstrated when comparing canine and human colorectal cancer, and tumours taken from these two species were allocated according to the histological subtype and not the species [34].

As is the case in human digestive system malignancies, perturbations in the tumour suppressing gene adenomatous polyposis coli (APC) have been found to be present in colonic adenocarcinomas of dogs [40]. Y o u m a n s and colleagues [40] analysed the results of exon-sequencing performed in 23 spontaneously developed canine colorectal tumours, including eight benign adenomatous polyps and 13 invasive intestinal adenocarcinomas. Mutations in the APC were the most frequently identified genetic alterations noted in both adenomas and adenocarcinomas. Large deletions of ≥10 bases as well as single and two base mutations were identified in approximately 70 % of both benign and malignant canine colonic tumours. Many of these genetic alterations were present in the proximity of the mutation cluster region. Besides being a very common genetic alteration, these results suggest that mutations in the APC are an early event in the process of carcinogenesis of colorectal epithelial tumours in dogs [40].

Not all molecular events driving tumorigenesis in dogs have yet been fully elucidated, and further research is required.

The adenoma to carcinoma sequence in canine colorectal tumours

Besides the interspecies homology seen when comparing malignant colorectal tumours in dogs with the corresponding lesions in humans, canine adenomatous polyps also share many homologies to analogous benign lesions in humans [28].

Stem cells of the colonic mucosa are present at the bottom of epithelial crypts, and they proliferate in this localization. Later, the daughter cells migrate into upper parts of the crypt where they lose their ability to divide, and they start to differentiate [10]. This process of proliferation and differentiation is tightly controlled by the wingless-related integration site (WNT) signalling pathway and involves the β-catenin protein [24].

Mutations leading to disturbances in the WNT molecular signalling axis are of major importance in human adenoma formation and colorectal carcinogenesis [41]. Considering the molecular characteristics of colorectal adenomatous polyps in dogs, cytoplasmic and abnormal nuclear accumulation of β-catenin protein was demonstrated immunohistochemically in tumour cells of canine colorectal adenomas [24]. These results suggest that dysregulation in the WNT signalling pathway, as in humans, is an important pathogenetic mechanism involved in the process of canine colorectal adenoma formation and progression [24]. Similar to the well documented adenoma to carcinoma progression in humans, canine colonic adenomas show a tendency to progress to invasive adenocarcinomas through malignant transformation [12]. These precursor lesions progressively acquire genetic alterations, which confer survival advantages and invasive potential of the tumour cells of the adenomatous lesion [35]. However, the molecular events driving carcinogenesis in canine adeno-

matous polyps seem to differ, at least partially, from those in humans because the acquisition of Tp53 mutations is not a common event in the case of colorectal adenomas in dogs [39]. Overall, high-grade dysplastic features can develop in canine adenomatous polyps, which progress into frank malignancy in 17 % to 50 % of this species [35].

Not all invasive adenocarcinomas of the large intestine in dogs develop from benign adenomatous polyps [31]. Beside the described adenoma to carcinoma sequel, another important concept of carcinogenesis in the alimentary tract is the *de novo* carcinoma theory [20]. Based on this cancer formation concept, the primary non-invasive tumour lesions have a macroscopically flat appearance and remain in this phenotypical form even after progression of the lesion and the development of microinvasion into the lamina propria [22, 31]. Since no grossly visible prominent polypoid lesions are identified in these cases, such lesions are easily missed using routine visualization methods [20]. Furthermore, the biological behaviour seems to differ in the case of macroscopically flat-shaped colorectal adenocarcinomas, which are reported to be highly malignant, even though the tumours are relatively small [15, 20].

Histological features of canine colorectal tumours

Several types of malignant tumours in the colonic and rectal area can be distinguished according to the WHO Histological Classification of Tumours of the Alimentary System of Domestic Animals [13]. Using this classification, epithelial intestinal malignancies can be divided into: the acinar (tubular) adenocarcinoma, the mucinous adenocarcinoma, the signet-ring cell adenocarcinoma, the papillary adenocarcinoma, the undifferentiated carcinoma category, and the adenosquamous carcinomas [13]. As is the case in large intestine epithelial malignancies of humans, intratumoural histological heterogeneity is a very common phenomenon in canine colorectal adenocarcinomas. The most common form of mixed adenocarcinoma is the combination of acinar (tubular) and papillary morphology. The presence of various growth patterns in a given adenocarcinoma case represents a challenge for accurate histopathological classification [31]. Considering other epithelial malignancies, pure squamous cell carcinomas in the large intestines of dogs are even rarer than in humans, with very few reported cases [19, 26].

S a i t o et al. [31] analysed the biological behaviour and prognostic implications of the various histological subtypes of tubular (acinar), papillary and mixed tubulopapillary subtypes of intestinal adenocarcinomas. No significant differences in the incidence rate of invasion and metastasis were noted. However, they suggested that dividing colorectal epithelial malignancies into polypoid and non-polypoid categories has more prognostic relevance. In their study, they demonstrated invasion and metastasis in 21 % of the cases of the polypoid type and 100 % of the non-polypoid type of adenocarcinomas. Canine adenocarcinomas with a non-polypoid growth pattern may be therefore considered as a more aggressive malignant subtype than polypoid growing tumours [31].

Clinical signs and diagnosis of canine colorectal tumours

Because of the interspecies similarities in the sense of anatomical localization and gross morphological features, perhaps not surprisingly the clinical signs related to the tumour growth are similar when comparing canine with human colorectal adenocarcinomas [1, 29].

Clinical signs related to the presence of neoplasia occluding the proximal parts of the colon are in the form of anorexia, vomiting, bleeding, weight loss and intussusception. Clinical signs related to the growth of adenocarcinomas in the rectum tend to be different [1, 25]. Classically described in German shepherd dogs, the cardinal clinical signs of rectal adenocarcinoma are constipation, tenesmus, dyschezia, and haematochezia [8]. The faeces in such affected dogs are often described as “ribbon-like” and such an appearance is caused by narrowing of the rectal lumen because of the progressively enlarging tumour mass [1].

Considering the diagnosis of tumorous masses in the rectum of dogs, digital examination is easy to perform and is known to be the most sensitive method used to detect these masses [5]. In early rectal masses, digital examination is known to be more sensitive than ultrasonography and proctoscopy [5, 6]. If large rectal masses and lesions characterized by deep infiltration are noted, then proctoscopy with subsequent biopsy is indicated [1]. In the case of rectal tumours, rectal proctoscopy has been found to be superior to flexible endoscopy. Besides providing better visualization, rigid proctoscopy allows the veterinary physician to use rigid biopsy forceps [38]. Ample tissue samples, which should also contain parts of the submucosa, can be obtained with the proper use of rigid biopsy forceps [1]. Such deep biopsy samples are of major im-

portance to properly differentiate benign adenomas from invasive colorectal adenocarcinomas, because both benign and malignant lesions can manifest macroscopically with the same gross appearance [5].

Compared with rectal tumorous masses, invasive adenocarcinomas localized in the ascending or descending colon are not readily accessible and are therefore more difficult to diagnose [5]. If the tumour is localized in the more distal parts of the descending colon, rigid proctoscopy may be performed [38]. However, this method does not provide access to the transverse and proximal colon in dogs. Colonoscopy may be indicated when there is suspicion of a neoplastic process in these areas [5]. Colonoscopy has the disadvantage that it requires cleaning the colon of faecal material and the use of anaesthesia of the patient [4]. To limit the number of colonoscopies required, abdominal ultrasonography is indicated before the performance of this procedure. Abdominal ultrasonography can detect lymphadenopathy and more obvious signs of widespread metastatic involvement in the abdominal area [1, 5, 38].

CONCLUSIONS

Dogs are an attractive animal model for the oncological study of colorectal cancer because of the interspecies similarities which allow us to recapitulate molecular etiopathogenesis, morphological characteristics and clinical features in humans. Furthermore, intestinal adenocarcinomas in dogs are naturally occurring heterogeneous cancers, which share the characteristics of sporadic human colon cancer and therefore fit better for the purpose of efficient oncological study than most xenografts or genetically modified rodent models. However, not all molecular events driving carcinogenesis in dogs are yet fully elucidated, and further research is required.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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