Relevance of chromosome 13 aberrations in canine tumours

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Summary
For human tumours there are many reports documenting the correlation between chromosome aberrations and tumour entities. Due to the complex canine karyotypic pattern (78 chromosomes), cytogenetic studies of tumours of the dog are rare. However, the reports in the literature show, that canine chromosome 13 (CFA 13) is predominantly involved in chromosomal changes. Interestingly, CFA 13 shows high homology to regions on the human chromosomes 4 (HSA 4) and 8 (HSA 8), which harbour the proto-oncogenes c-KIT and c-MYC. Both of these genes are involved in the development and progression of some human and canine tumour diseases.

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Tumour cytogenetic analyses in dogs

Tumour cytogenetic analyses are important for the diagnostic, prognostic, and therapeutic control of human cancer diseases (13, 26). Currently, more than 60,500 cases of tumours with chromosomal aberrations are listed in the “Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer” (25). Humans and dogs share companionship and living space and interestingly a similar genetic make-up. Both develop comparable diseases, including the same types of cancer. In senior dogs cancer is a very common disease and one of the leading causes of death. Compared to other animal models, the dog has proven to be invaluable in research and development on cancer drugs, as dogs naturally develop cancers that share many characteristics with human malignancies (18). However, due to the complicated canine karyotype, cytogenetic analyses of tumours of the dog are challenging.

The karyotype of the dog consists of 76 acrocentric chromosomes, similar in size, shape, and banding pattern and the metacentric X- and Y-chromosomes. Figure 1 shows a comparison between human (a) and canine (b) chromosomes, underlining the difficulties of “karyotyping the dog”. An international standard nomenclature for the canine karyotype, comparable to the 40 years ago firstly proposed “International System for Chromosome Nomenclature” for the human karyotype (17), has been proposed in 1996 (32, 36). In spite of the late availability of a canine complete nomenclature, cytogenetic analyses of different canine neoplasms have been performed and revealed that akin to the situation in human tumours, several tumours of the dog are characterised by clonal aberrations (e. g. [3, 15, 23, 27–28, 30, 33]).

Canine chromosome 13: frequent target for chromosomal aberrations

A literature survey shows that the canine chromosome 13 is preferentially involved in clonal aberrations. Early reports describing cytogenetic investigations of a canine osteoid sarcoma and a canine mammary carcinoma revealed the existence of isochromosome 13 accompanied by other karyotypic changes, whereas in a canine osteoid chondrosarcoma isochromosome 13 was the sole cytogenetic abnormality (22, 23). Chromosome analyses on 61 dogs with lymphosarcoma performed by Hahn et al. (14) showed trisomy 13
in 15 cases. It was demonstrated that dogs with tumours displaying a trisomy 13 as the primary aberration had a longer remission free period and survival compared to dogs with complex karyotypic changes. In addition, dogs with trisomy 13 responded better to an adriamycin or epirubicin therapy (14). In a previous study we were able to describe a trisomy 13 along with several other chromosomal aberrations and a partial trisomy 13 as the sole abnormality both occurring in canine lymphomas (40). Comparative genomic hybridization analyses performed by Thomas et al. (38) revealed that the gain of chromosome 13 was the most commonly observed aberration in canine multicentric lymphomas. Just recently we described a polysomy 13 as the sole cytogenetic deviation in a case of canine prostate carcinoma and a polysomy 13 along with complex karyotypic changes in two other cases of canine prostate cancer (31, 41). Upon these results, it was hypothesized that additional copies of canine chromosome 13 might be involved in the progression as well as in the initiation of prostate tumour disease (31). Moreover, polysomy 13 in combination with centric fusions of chromosomes 13 most probably is a characteristic cytogenetic finding in canine prostatic carcinoma (Fig. 2). A previous report demonstrated that these fusions might result from stable telomeric associations (34). Fusions between acrocentric chromosomes are a frequent event during tumourigenesis in the dog (3, 15, 24). Thus, the event of the fusion of two chromosomes 13 alone might play an important role in the development of canine tumours.

### Genes on canine chromosome 13

Interestingly, reciprocal chromosome painting (5), comparative genome data (4) and in silico analyses via the “Evolution Highway” (8) indicated that the canine chromosome 13 (CFA 13) shares high homology to the terminal region of the long arm of the human chromosome HSA 8 (8q23-qtel) and to the centromeric region of the long arm of HSA 4 (4prox-qprox) (Fig. 1, Fig. 3). The former of these human chromosomal regions harbours the c-MYC oncogene, the latter the c-KIT oncogene.

c-MYC was one of the first oncogenes identified and has subsequently been linked with a wide range of human cancers, e.g. haematopoietic tumours (7), tumours of the bladder (21), the breast (2), prostate cancer (6), and osteosarcomas (35). Reports evaluating the role of c-MYC in canine tumourigenesis are still rare, however correlations have been described for example in canine transmissible venereal tumour (1), in canine plasma cell tumours (10),
Clinical relevance

Numerical aberrations of canine chromosome 13 can be observed in several canine tumours. Therefore it is likely to assume that the canine chromosome 13 contains a gene or gene clusters which are involved in the multistep cascade of tumour initiation and progression. Human chromosomes (HSA) 8q and 4q and the canine chromosome (CFA) 13 share high homology, thus it is suggested that a conserved area on these chromosomes is involved in tumourigenesis in both species.

Thus cytogenetic and molecular genetic studies concentrating on chromosome 13 will not only help to understand the role of CFA 13 in the tumourigenesis in dogs but will also be relevant for human tumour research.

Conflict of interest

The authors declare that they do not have any conflict of interest.

References


5. Breen M, Thomas R, Binna MM, Carter NP, Langford GF. Reciprocal chromosome painting reveals detailed regions of conserved synteny between the chromosomes (HSA) 8q and 4q and the canine chromosome (CFA) 13 in mammary tumours of the dog (16), and in canine osteosarcoma (19). For the second oncogene c-KIT, located on human chromosome 4, expression has been described for a variety of human tumour entities, e.g. malignant melanomas (11), breast and lung cancer (20, 29). The involvement of c-KIT in the development and progression of canine cancer, e.g. in canine malignant hemangiosarcoma (9), in mast cell tumours of the dog (12) and in canine leukaemias (39), has also been documented.

The recurrent gain of CFA 13 observed in different canine tumour entities underlines the importance to examine the involvement of c-MYC and c-KIT in malignancies of the dog. Certainly there are many more genes localised on canine chromosome 13, which are and might be involved in the multistep cascade of tumour initiators and promoters. Interestingly, a very recent report by Thomas et al. (37) showed that in contrast to current research in human lymphoma, where numerous genes have been identified as possibly having a relationship to the cancer, there were only a few genes involved with lymphoma that were shared by dogs and humans. The authors concluded that while both dogs and humans have comparable disease at the clinical and cellular level, the genetic changes associated with the same tumours are much less complex in the dog and it is suggested to focus the studies on the genetic changes that are shared by dogs and human.

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