Characterization of the Canine HMGB1 Gene (5-Sep-2003)

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As witnessed by a number of recent articles a growing number of scientists predict that human genetics will be "going to the dogs" in this century. Due to the emerging advantages of numerous canine diseases as a genetic model for human orthologs, the dog could join the mouse as the species of choice to unravel genetic mechanisms of e.g., cancer predisposition, development, and progression.

A very interesting gene in terms of oncology is the high mobility group protein gene B1 (HMGB1). This best analyzed member of the HMGB protein family, HMGB1 (synonymously known as HMG1 or amphoterin), can modify chromatin structure by bending DNA thus influencing the transcription of a number of target genes. Beside its function as an architectural transcription factor, HMGB1 can also be secreted by certain cells, e.g., macrophages. As an extracellular protein HMGB1 is a ligand for the receptor for advanced glycation end products (RAGE) thus activating key cell signaling pathways, such as p38MAPK, JNK, and p42/p44MAPK and playing an important role in inflammation and tumor metastasis. HMGB1 gene expression can be induced by estrogens in breast cancer MCF-7 cells probably due to an upregulation of the gene so that HMGB1 itself can be considered an estrogen-responsive gene. Additionally, it has been shown that HMGB1 is able to bind to cisplatin-DNA-adducts and sensitizes cancer cells to cisplatin by shielding its major DNA adducts from nucleotide excision repair. By causing an overexpression of HMGB1 estrogen can significantly increase the effect of cisplatin. This finding has led to the conclusion that estrogen treatment prior to cisplatin therapy may sensitize the cancer cells against that drug.

The enlightenment of the canine molecular structure could permit new therapeutic approaches for the dog. In our studies we characterized the canine gene HMGB1 on various levels. The canine cDNA sequence consists of 2236 bp spanning five exons with a total homology of 90.8% to its human counterpart. The genomic structure of the gene consists of the five exons and four introns of which exon 1 (76 bp) and a contig spanning exon 2 - exon 5 (3959 bp) were characterized. Homology comparison to the human ortholog revealed 98.7% similarity for exon 1 and 73.9% for the contig spanning exon 2 - exon 5. The protein deduced from the generated cDNA sequence is a 215 amino acid (AA) molecule with a weight of 24892.67 Daltons. Homology comparison to the human counterpart showed 100% homology of the molecules. The chromosomal locus was mapped by FISH to CFA 25. Expression analyses by Northern blot revealed two transcripts of approx. 1.4 and 2.4 kb in various tissues.

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