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Canine insulinoma as a model for studying molecular genetics of tumorigenesis and metastasis

Insulinoma is the most frequently diagnosed neuroendocrine pancreatic tumor of dogs and humans. Most insulinomas of humans are treated effectively by surgical excision. However, a subset of human insulinomas exhibits cellular characteristics and clinical behavior consistent with malignancy and these are referred to as ‘malignant insulinoma’. Tumors of the latter type are therapeutically challenging and difficulties are magnified because surgical excision of malignant insulinoma is rarely complete and recurrence is likely, features which conspire to decrease survival times in affected patients.

In the dog, the biologic course of insulinoma resembles that of malignant insulinoma in humans. Morbidity in dogs with insulinoma is usually due to the functional capacity of the tumor rather than signs related to its physical presence. Until hypoglycemia becomes apparent, the tumor with its high metastatic potential may elude diagnosis. In the dog, as in humans, surgery along with post-operative chemotherapy is still the recommended approach when possible. Despite the recent observation that intensive management improves survival times (Polton et al., 2007), the high prevalence of distant metastasis at diagnosis limits therapeutic options and translates to a poor long term prognosis for affected dogs. Novel approaches are needed to improve diagnosis, prognosis and therapy for canine and human insulinomas.
Despite the clinical challenges associated with definitive treatment of canine insulinoma, it is a well defined tumor syndrome that offers excellent opportunities for molecular study of basic tumor biology. A series of recent papers by Dr Floryne Buishand and colleagues of Utrecht and Maastricht Universities, including the study that appears in this issue of Veterinary Journal (Buishand et al., 2013), both contribute to our understanding of the molecular genetics of canine insulinoma and serve to highlight the use of canine insulinoma as a valuable research model for the study of tumorigenesis and metastasis.

Insulinomas in humans can occur as part of an inherited syndrome, designated multiple endocrine neoplasm type 1 (MEN1), but the majority of human insulinomas arise sporadically and are due to an inherited genetic mutation (Jonkers et al., 2007). Although there are reports of MEN-like syndromes in dogs, including one dog with an insulinoma (Kiupel et al., 2000), the role of MEN1, the gene responsible for the MEN syndrome, has not yet been investigated in canine insulinoma. However, no MEN1 coding mutations were found in a study of Keeshonds with familial hyperparathyroidism (Skelly and Franklin, 2007). As in humans, the majority of insulinomas occurring in dogs are considered to be ‘sporadic’. The genetic alterations in sporadic tumors are caused by somatic mutations, but the precise genes and the molecular mechanisms involved that promote unrestrained cell growth and metastasis remain poorly defined.
Microarray studies of human insulinomas have revealed changes in expression of genes involved in DNA repair, apoptosis and transcriptional regulation pathways (Jonkers et al., 2007). In this issue, Buishand et al. (2013) used microarray analysis to investigate the expression of a large number of genes (>10,000) in primary canine insulinomas and their metastases. Pathway analysis revealed down-regulation of pathways involved in DNA damage repair, including breast cancer type 1 (BRCA1), which is also abnormal in some human insulinomas, and pathways involved in cell cycle regulation, including the ataxia telangiectasia mutated and Rad3-related (ATM/ATR) pathway, which regulates entry into the cell cycle S phase. Substantial differences in gene expression were also noted between primary insulinomas and their corresponding metastases. Interestingly, a similar study of human insulinomas did not find differences in gene expression profiles when primary insulinomas and their metastasis were compared (Capurso et al., 2006).

Several other features of canine insulinomas identified by Buishand and colleagues, such as expression of growth hormone (Buishand et al., 2012) and, in the current study, co-expression of genes typically expressed in the exocrine pancreas (Buishand et al., 2013), are not frequently observed in human insulinomas or have not yet been fully investigated (Wulbrand et al., 2000; Ordonez, 2001).

It is safe to assert that new targets for insulinoma therapy may be identified by uncovering the pathways that permit unregulated growth and that facilitate distant metastasis of tumor cells. While extrapolation of knowledge from human studies is often the source of new approaches in veterinary medicine, the highlighted differences
between canine and human insulinoma emphasize the need for focused studies of canine
tumors. The work of Buishand and colleagues represents an important step forward in
understanding the molecular genetics of canine insulinoma, particularly how these
mechanisms dictate tumor growth and metastasis.

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References

Gene expression profiling of primary canine insulinomas and their metastases.

Buishand, F.O., van Erp MG, Groenveld HA, Mol JA, Kik M, Robben JH, Kooistra HS,

Capurso, G., Lattimore, S., Crnogorac-Jurcevic, T., Panzuto, F., Milione, M., Bhakta,
V., Campanini, N., Swift, S.M., Bordi, C., Delle Fave, G., Lemoine, N.R.,
2006. Gene expression profiles of progressive pancreatic endocrine tumours
and their liver metastases reveal potential novel markers and therapeutic
targets. Endocrine Related Cancer 13, 541-558.

insulinoma tumorigenesis. Biochimica et Biophysica Acta 1775, 313-332.

endocrine neoplasia in a dog. Journal of Comparative Pathology 123, 210-217.

Ultrastructural Pathology 25, 485-495.

retrospective cohort of 28 dogs with insulinoma. Journal of Small Animal
Practice 48, 151-156.