The Veterinary Journal 257 (2020) 105453

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Short communication

Carnitine palmitoyltransferase 1 A expression profile in canine mammary tumors

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ARTICLE INFO

Article history:
Accepted 27 March 2020

Keywords:
Canine mammary tumors
Fatty acid β-oxidation
Immunohistochemistry
Metabolism
Mitochondria

ABSTRACT

Genetic alterations and/or epigenetic modifications occur frequently in the majority of cancer cells. In addition to playing a crucial role as promoters of tumorigenesis, these processes can also generate metabolic pathways that are different from those in normal cells. Besides the Warburg effect, an alteration in lipid metabolism is also found in cancer cells. Thus, elucidation of the regulators involved in this metabolic reprogramming might provide tools for diagnosis, prognosis, and ultimately treatment of canine mammary tumours (CMTs) in particular. One such regulator is carnitine palmitoyltransferase 1A (CPT1A), which is involved in transportation of long-chain fatty acids into the mitochondrial matrix for beta-oxidation, thereby providing an alternative pathway for the generation of energy for tumour growth and development. In this study, the canine cell lines MDCK, CMT-U309, CMT-U27, and P114 were used as in vitro models for western blot and quantitative real-time polymerase chain reaction (qRT-PCR) analyses. Furthermore, western blot and immunohistochemistry were carried out to evaluate CPT1A protein expression in the CMT specimens. The CPT1A protein and mRNA expression levels were increased in the CMT cell lines relative to their levels in normal epithelial cells. Moreover, increased CPT1A expression levels were found in the CMT tissues, being inversely correlated with the tumour differentiation grade. However, additional studies are required to further specify the role of CPT1A in CMTs.

Spontaneous canine mammary tumours (CMTs) represent a useful animal model for studying the molecular mechanisms underlying malignant transformation (Visan et al., 2016) and they may be helpful for improving the prognosis and treatment of human breast cancer (HBC; Abdelmegeed and Mohammed, 2018). During malignant transformation, most cancer cells reprogram their metabolic pathways in order to obtain the energy and metabolites required for rapid growth and division (Locasale and Cantley, 2011; Lunt and Vander Heiden, 2011; Slavov et al., 2014). The reprogramming of energy metabolism is considered a hallmark of cancer (Hanahan and Weinberg, 2011). Although glycolytic dependency (Warburg effect) in tumours has been well documented (Koppenol et al., 2011), it is not known how cancer cells use other energy sources (e.g. lipids) to satisfy their metabolic demands (Melone et al., 2018). Lipids play a pivotal role in cancer proliferation because they can be broken down through fatty acid beta-oxidation (FAO) to provide energy after their cellular uptake (Nomura et al., 2010; Nieman et al., 2011; Nomura and Cravatt, 2013). Carnitine palmitoyltransferase 1A (CPT1A), an enzyme localised on the outer mitochondrial membrane, plays a key role in FAO by converting acyl-CoA into acylcarnitine. The latter facilitates the transfer of long-chain fatty acids (e.g. palmitate) into the mitochondrial matrix for FAO (Schoors et al., 2015). CPT1A is overexpressed in many human tumours, including breast cancer, where it represents a key target for pharmacotherapy (Samudio et al., 2010; Schlaepfer et al., 2014; Park et al., 2016). CPT1A inhibitors (Etomoxir and ST1326) enhance the apoptosis, slow down the proliferation, and decrease the chemoresistance of cancer cells (Samudio et al., 2010; Gugiatti et al., 2018). To the best of our knowledge, no data are yet available on the expression of CPT1A in CMTs. Therefore, the aims of the present study were 1) to

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http://dx.doi.org/10.1016/j.tvjl.2020.105453
1090-0233/

evaluate the expression of CPT1A in three CMT cell lines using western blot (WB) and quantitative real time polymerase chain reaction (qRT-PCR) assays and in 47 CMT tissues using western blot (WB) and immunohistochemistry (IHC) analyses; and 2) to compare CPT1A expression levels among normal mammary gland (NMG) tissues, benign tumours, and malignant tumours of different histological grades (Table 1). For a detailed description of the experimental procedures, see Supplementary Materials and methods. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Using the WB assay, we assessed CPT1A protein expression in four canine cell lines and found increased levels of this protein in all three CMT cell lines (CMT-U309, P114, and CMT-U27) relative to those in the immortalised normal epithelial cell line MDCK (Fig. 1a, left panel); the usefulness of this cell line as a control has been reported previously (Altamura et al., 2017). Specifically, the CPT1A levels were increased 7.31-, 5.26-, and 7.53-fold in the CMT-U309, P114, and CMT-U27 cells, respectively (Fig. 1b, right panel). We then investigated the expression of CPT1A by qRT-PCR, using specific primers for the protein, and obtained similar results. In particular, the CPT1A mRNA expression level increased 15.1-, 8.8-, and 12.3-fold in the CMT-U309, P114, and CMT-U27 cells, respectively, over that in the MDCK cells (Fig. 1c). Considering the positive results on the CMT cell lines, we carried out WB analysis on canine NMG and CMT tissues and found the CPT1A expression levels to be 55-fold lower than those in the cancerous

Table 1
Main characteristics of normal and neoplastic canine mammary tissues and carnitine palmitoyltransferase 1A (CPT1A) immunoreactivity cells, staining intensity and immunoreactive (IR) score.[a]

Case number	Breed	Age (years)	Histotype	Tumor grade	CPT1A immunoreactive cells (%)	Staining intensity	IR score
1	Mixed breed	9	Normal mammary gland	Normal gland	51.2	2	6
2	German shepherd	7	Normal mammary gland	Normal gland	48.4	3	9
3	Mixed breed	4	Normal mammary gland	Normal gland	60.3	2	8
4	Poodle	11	Normal mammary gland	Normal gland	0	0	0
5	Jack Russel terrier	5	Normal mammary gland	Normal gland	57.2	3	9
6	Mixed breed	9	Normal mammary gland	Normal gland	0	0	0
7	American terrier	6	Adenoma simple	Benign	75	3	12
8	Mixed breed	11	Complex adenoma	Benign	56.4	3	9
9	Mixed breed	8	Adenoma simple	Benign	70.8	2	8
10	Mixed breed	9	Benign mixed tumor	Benign	52.3	3	6
11	Yorkshire terrier	10	Complex adenoma	Benign	52.6	3	9
12	Mixed breed	9	Tubular carcinoma	1	27.5	3	6
13	Beagle	6	Simple carcinoma	1	78.4	3	12
14	Cocker spaniel	9	Tubulopapillary carcinoma	1	75.4	3	12
15	Mixed breed	14	Tubular carcinoma	1	70.4	3	12
16	Mixed breed	8	Tubulopapillary carcinoma	1	28.0	2	4
17	Mixed breed	11	Simple carcinoma	1	51.9	2	6
18	Shih tzu	9	Tubulopapillary carcinoma	1	87.5	3	12
19	Irish setter	7	Mixed type carcinoma	1	90.0	3	12
20	Yorkshire terrier	8	Complex type carcinoma	1	79.2	2	8
21	Pinscher	9	Complex type carcinoma	1	69.5	3	12
22	Yorkshire terrier	13	Complex type carcinoma	1	47.9	3	9
23	Jack Russel terrier	3	Mixed type carcinoma	1	52.4	3	9
24	Yorkshire terrier	8	Complex type carcinoma	1	84.3	3	12
25	Mixed breed	7	Tubulopapillary carcinoma	1	54.5	3	9
26	Mixed breed	9	Cystic papillary carcinoma	2	39.2	2	6
27	Epagneul Breton	10	Tubulopapillary carcinoma	2	12.3	2	4
28	Mixed breed	6	Mixed type carcinoma	2	47.5	2	6
29	Cocker spaniel	10	Tubular carcinoma	2	59.8	3	9
30	Mixed breed	11	Tubular carcinoma	2	65.9	2	8
31	Mixed breed	9	Solid carcinoma	2	32.1	2	6
32	Mixed breed	9	Tubular carcinoma	2	25.1	2	6
33	Mixed breed	13	Tubular carcinoma	2	25.1	2	4
34	Shih tzu	9	Tubular carcinoma	2	21.2	3	6
35	Mixed breed	9	Tubulopapillary carcinoma	2	22.4	3	6
36	Cocker spaniel	6	Complex type carcinoma	2	21.7	1	2
37	Mixed breed	10	Tubulopapillary carcinoma	2	65.7	3	12
38	Mixed breed	13	Tubular carcinoma	2	72.0	3	12
39	Poodle	15	Complex type carcinoma	2	90.0	2	8
40	Mixed breed	13	Tubular carcinoma	3	51.9	2	6
41	Mixed breed	12	Tubular carcinoma	3	12.0	3	6
42	Mixed breed	11	Complex type carcinoma	3	6.4	2	2
43	Shih tzu	9	Complex type carcinoma	3	7.4	1	1
44	Mixed breed	12	Mixed type carcinoma	3	10.2	1	2
45	Greyhound	9	Spindle cell carcinoma	3	5.7	3	3
46	Mixed breed	13	Adenosquamous carcinoma	3	4.7	1	1
47	Mixed breed	9	Carcinoma and malignant myopithelioma	3	28.4	2	4
48	Pinscher	7	Complex type carcinoma	3	8.2	1	1
49	Mixed breed	13	Mixed type carcinoma	3	27.7	3	6
50	Siberian husky	11	Comedocarcinoma	3	5.6	1	1
51	German shepherd	4	Tubular carcinoma	3	32.6	1	3
52	Beagle	6	Tubular carcinoma	3	31.0	2	6

[a] The immunoreactive (IR) score gives a range of 0–12 as a product of multiplication between percentage of CPT1A immunostained cells (score: 0–4) and staining intensity score (0–3). See Supplementary materials and methods for details.

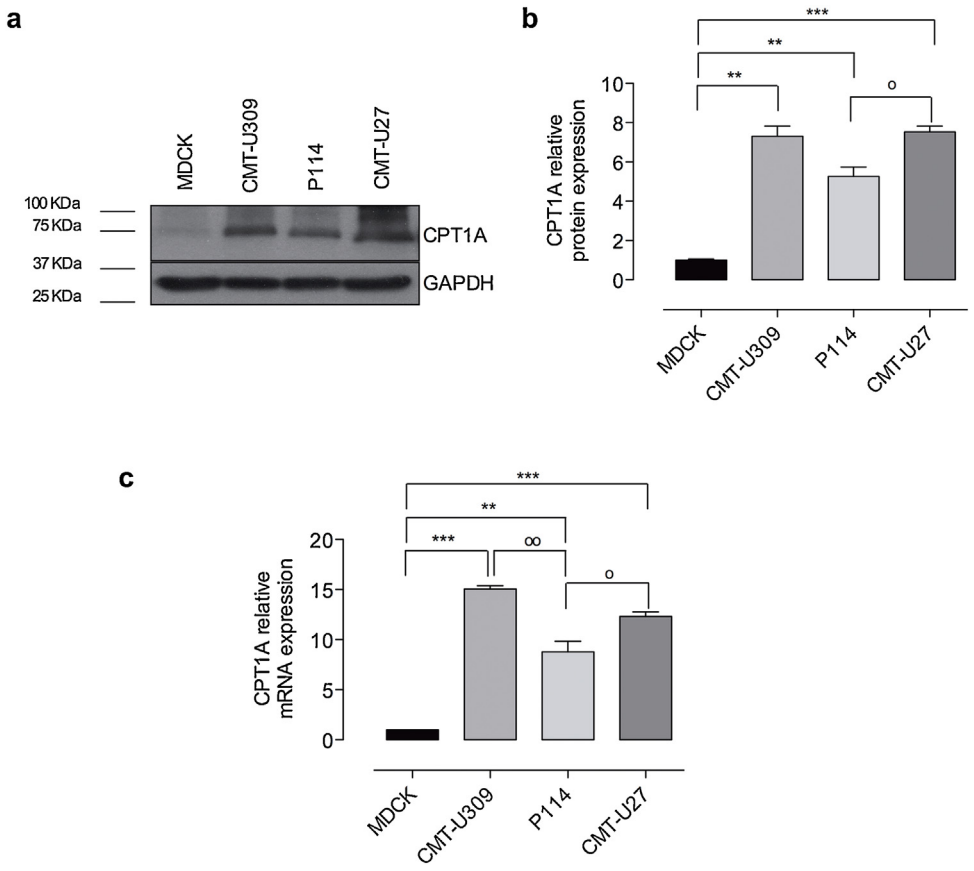

Fig. 1. Expression of carnitine palmitoyltransferase 1A (CPT1A) protein and mRNA in canine mammary cell lines. a) Representative western blot analysis and b) densitometric values of CPT1A protein expression in normal epithelial cells (MDCK) and three canine mammary tumor (CMT) cells (CMT-U309, P114 and CMT-U27). GAPDH was used as an internal control to verify equal protein loading. Each bar represents the mean ± SEM of repeated independent experiments (ANOVA) *$P < 0.05$ ** $P < 0.01$ and *** $P < 0.001$ vs. control (MDCK cells); o $P < 0.05$ vs. P114 cells b) Representative qRT-PCR analysis of CPT1A mRNA expression in normal epithelial cells (MDCK) and three CMT cells (CMT-U309, P114 and CMT-U27). Each bar represents the mean ± SEM of repeated independent experiments (ANOVA);** $P < 0.01$ *** $P < 0.001$ vs. control (MDCK cells); oo $P < 0.01$, o $P < 0.05$ vs. P114 cells.

tissues (Fig. 2a,b). According to the IHC results, only ductal and lobular epithelial cells showed positive CPT1A immunostaining, both in the NMGs and CMTs. In fact, the myoepithelial cells were negative for staining, whereas the inflammatory cells showed weak CPT1A immunoreactivity; that is, four out of six NMGs (67%) showed moderate immunostaining (mean immunoreactivity [IR] score = 4.83 ± 1.60, range 0–9), characterised by few and small cytoplasmic granules (Fig. 2c). All benign tumours (5/5; 100%) showed strong immunostaining (mean IR score = 8.80 ± 0.970), with few and small cytoplasmic granules (Fig. 2d). All well-differentiated (G1) carcinomas (14/14; 100%) displayed strong CPT1A immunoreactivity (mean IR score = 9.43 ± 0.724, range 4–12), characterised by large granules which were present mostly throughout the cytoplasm and in the intra-tumoral areas (Fig. 2e). Although all moderately differentiated (G2) carcinomas (14/14; 100%) also showed strong immunoreactivity for CPT1A (mean IR score = 6.79 ± 0.757, range 2–12), the protein was restricted to regions where the mammary glandular morphology was still preserved (Fig. 2f). Thirteen out of 14 poorly differentiated (G3) carcinomas (92%; mean IR score = 3.00 ± 0.593, range 0–6) stained only weakly for CPT1A, albeit moderate immunostaining was present in the phenotypically less aggressive counterparts (Fig. 2g). Interestingly, in four out of 14 G3 carcinomas (29%), strong CPT1A immunoreactivity was observed only in the neoplastic cells that were infiltrating the surrounding tissue (Fig. 2h). Based on a semi-quantitative assessment of the CPT1A immunoreactive cells, the CPT1A protein expression levels correlated inversely with the degree of tumour differentiation (Fig. 2i).

In this study, we have evaluated for the first time the expression of CPT1A in CMT cell lines and tissues. We found higher CPT1A mRNA and protein expression levels in the CMT cell lines than in the control cells. This is consistent with previous studies which have reported an increase in the CPT1A mRNA and protein expression levels in HBC cells (Linher-Melville et al., 2011; Balaban et al., 2017). It has also been reported that CPT1A is overexpressed in several other human malignancies originating from different tissues (Liu, 2006; Caro et al., 2012; Camarda et al., 2016; Padanad et al., 2016). In accordance with those reports, and using WB analysis, we found that the CPT1A levels were higher in the CMT tissue samples than in the healthy control tissues, regardless of the tumour malignancy grade. According to the IHC results, CPT1A expression was higher in G1 carcinomas than in NMGs. By contrast, CPT1A protein expression correlated with a decrease in tumour differentiation; that is, less differentiated (G3) carcinomas expressed lower CPT1A levels than NMGs, benign tumours, and low (G1) to medium (G2) differentiated carcinomas. Consistent with these results, we also found reduced CPT1A levels in highly aggressive P114 cells, which were derived from an anaplastic canine tumour (Van Leeuwen et al., 1996). Our results share similarities with those of Louie et al. (2013), who demonstrated that aggressive cancer cells exhibited lower levels of CPT1A expression than their less aggressive counterparts, suggesting that

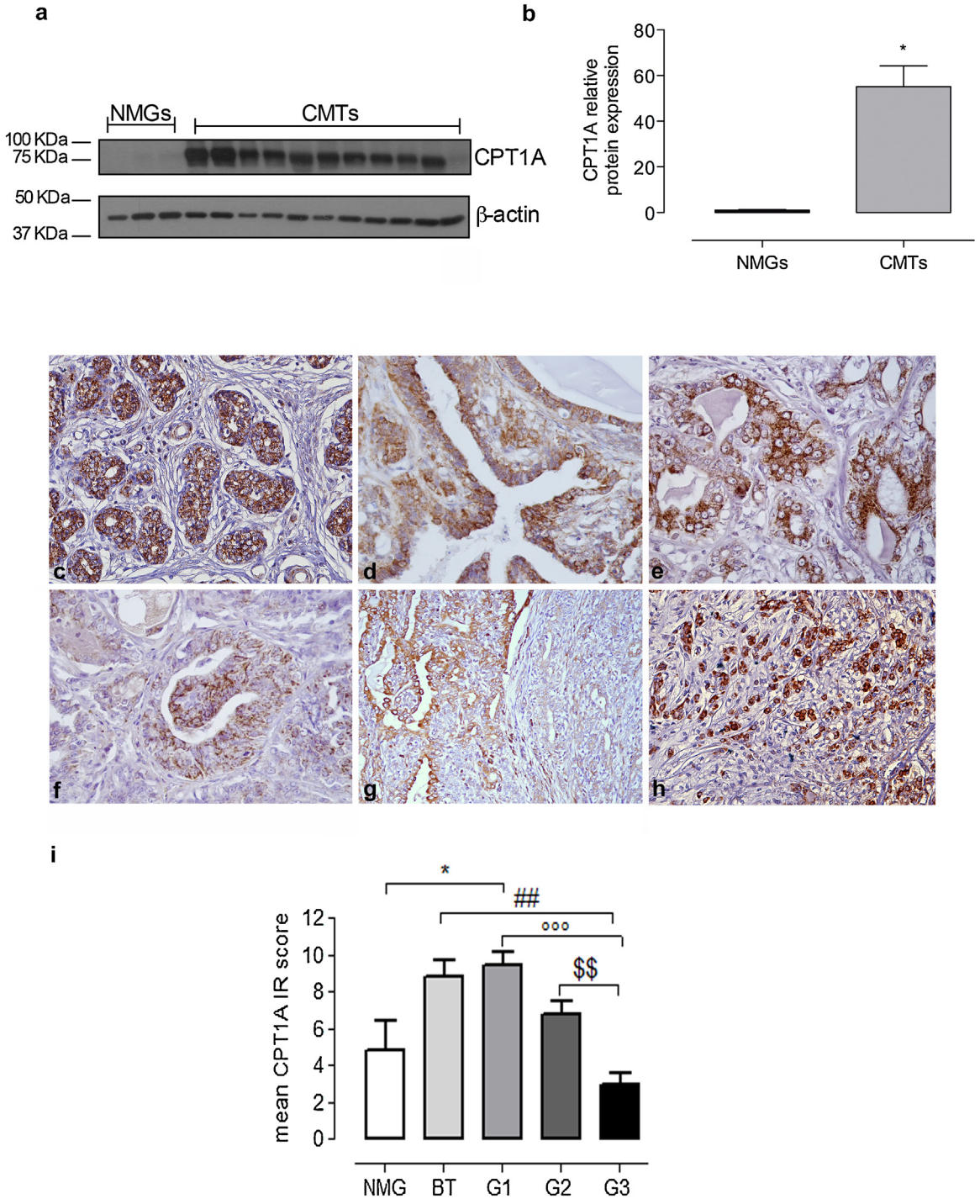

Fig. 2. Expression of carnitine palmitoyltransferase 1A (CPT1A) in canine mammary samples. a) Western blot analysis of CPT1A protein expression in three normal mammary glands (NMGs) vs. 11 canine mammary tumor tissues (CMTs). β-actin was used as control to verify equal protein loading. b) Graph shows the Mean ± SEM of relative CPT1A protein expression in CMTs vs. NMGs (Student's-*t*-test). c–h) Immunohistochemical labelling of CPT1A in canine normal and neoplastic mammary glands: c) NMG tissue. IR (immunoreactive) score = 8: CPT1A moderate immunostaining characterised by few and small cytoplasmic granules is evident in epithelial cells. Stromal and myoepithelial cells are negative. d) Simple adenoma case number 9, IR score = 8: strong CPT1A immunostaining characterised by few and small cytoplasmic granules is evident in 70.8% of neoplastic cells. e) G1 Mixed Type Carcinoma, case number 12, IR score = 9: CPT1A diffuse cytoplasmic strong immunostaining is observed in 52.4% of neoplastic epithelial cells and mainly localised in some neoplastic areas. f) G2 Cystic-Papillary Carcinoma, case number 15, IR score = 6: 39.2% neoplastic cells with moderate CPT1A immunostaining surround a central tubule-papillary area with strong CPT1A immunostaining. g) G3 Tubular, case number 41, IR score = 6: more differentiated neoplastic area with CPT1A strong immunostaining (left part) and less differentiated neoplastic area (right part) with CPT1A weak immunostaining are shown. h) G3 Mixed Type Carcinoma, case number 38, IR score = 6: strong CPT1A immunostaining in peripheric infiltrating neoplastic cells is shown. i) Graph shows the Mean ± SEM of Immunoreactive (IR) score for the expression of CPT1A in normal and tumoral samples with different malignancy grade (ANOVA) * $P < 0.05$ NMGs vs. G1 carcinomas; ## $P < 0.01$ between benign tumors vs. G3 carcinomas; °°° $P < 0.001$ between G1 vs. G3 carcinomas; $$ $P < 0.01$ between G2 vs. G3 carcinomas. NMG, normal mammary gland; BT, benign tumor; G1, grade 1 carcinomas; G2, grade 2 carcinomas; G3, grade 3 carcinomas.

CPT1A and FAO are attenuated during cancer progression in order to shunt fatty acids from the beta-oxidation pathway to generate more structural and oncogenic lipids (Louie et al., 2013). Therefore, the strong CPT1A expression observed in some aggressive G3 carcinoma cells that had infiltrated the surrounding tissue suggests that neoplastic cells use FAO as a source of energy for maintaining the mitochondrial membrane integrity (Delgoffe and Powell, 2015). By contrast, the decreased CPT1A protein expression level found in less differentiated tumours could be due to the generation of a stimulus by the adverse and hypoxic microenvironment which signals the cell to return to a glycolytic metabolic pathway, since aggressive breast cancer subtypes depend on increased glycolytic metabolism (Ahn et al., 2014; Liberti and Locasale, 2016). Moreover, it has also been reported that FAO may be relevant in tumours that grow in adipocyte-rich environments, such as HBC (Manabe et al., 2003). Therefore, we hypothesise that in the same way as HBC cells, CMT cells may use lipids stored in neighbouring adipocytes as a source of energy for FAO and as building blocks for tumour cell growth (Blucher and Stadler, 2017). In conclusion, our findings demonstrate for the first time the presence of CPT1A in canine NMGs and its increased expression in both spontaneous CMT samples and cancer cell lines as well as the inverse correlation between the CPT1A protein expression level and the tumour malignancy grade. These findings stress the need for more studies to characterise the functional role of CPT1A, with the ultimate goal being to determine its usefulness as a potential target for therapeutic application in cancers of humans and dogs.

Conflict of interest

None of the authors has any other financial or personal relationships that could inappropriately influence or bias the content of the paper.

Acknowledgements

The authors would like to thank Dr. Gerard Rutteman, Prof. Dr. Eva Hellmen and Dr. Serena Montagnaro for providing cell lines used in this study. Furthermore, the authors thank Dr. Serena Montagnaro for her contribution to statistical analysis, Prof. Gerhard Niebauer and Prof. Francesca Borrelli for critical review of the manuscript and Mr. Antonio Calamo for technical artwork. The authors received financial support from the research funding of the Department of Veterinary Medicine and Animal Production, University of Naples, Italy.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.tvjl.2020.105453.

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