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Intratumoral FoxP3 expression is associated with angiogenesis and prognosis in malignant canine mammary tumors

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ABSTRACT

The activity of regulatory T cells (Tregs) is closely associated with the expression of FoxP3 transcription factor. FoxP3 regulatory T cells (FoxP3Treg) have immunosuppressive properties and can work for prevention of harmful autoimmune responses, however can also interfere with beneficial anti-tumor immunity. In human breast cancer these cells play a crucial role in tumor progression. In canine mammary tumors (CMT) this topic is not well-documented. This study included 80 malignant CMT and studied, by immunohistochemistry, the intratumoral FoxP3 expression together with microvessel density (MVD), vascular endothelial growth factor (VEGF) and several clinicopathological characteristics. Abundant FoxP3Treg cells were associated with tumor necrosis ($p = 0.001$), high mitotic grade ($p < 0.001$), more marked nuclear polymorphism ($p = 0.001$), poor differentiation of tumors ($p < 0.001$), high histological grade of malignancy (HGM) ($p < 0.001$), presence of neoplastic intravascular emboli ($p < 0.001$) and presence of lymph node metastasis ($p < 0.001$). Intratumoral FoxP3 was correlated with MVD ($r = 0.827$; $p < 0.001$) and associated with VEGF ($p = 0.001$). Additionally tumors with abundant FoxP3Treg cells were associated with shorter overall survival (OS) time in univariate and multivariate analysis ($p < 0.001$ Kaplan–Meier curves and 7.97 hazard ratio, $p < 0.001$ Cox proportional hazard model). Results suggest that Treg cells play a role in CMT progression and may contribute to increased angiogenesis and aggression in these tumors. The association of intratumoral FoxP3 expression with shorter OS in multivariate analysis suggests the usefulness of Treg cells as an independent prognostic marker.

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1. Introduction

The activity of T regulatory cells (Tregs) is known to be closely associated with the expression of FoxP3 transcription factor (Campbell and Koch, 2011; Nishikawa and Sakaguchi, 2014). FoxP3 regulatory T cells (FoxP3Treg) are a distinct group of T lymphocytes that play an important role in the homeostasis of the immune system and in the modulation of the immune response. Tregs have emerged as key players in the development and maintenance of peripheral immune tolerance (Elkord et al., 2010; Piersma et al., 2008). Normally these cells can work for prevention of harmful autoimmune responses, however can also interfere with beneficial immune responses such as anti-tumor immunity (Elkord et al., 2010; Nishikawa and Sakaguchi, 2014; Whiteside, 2014). Tregs can secrete inhibitory cytokines, such as IL-10, TGF-β which induce the reduction of both CD8+ T lymphocytes and natural killer (NK) cells cytotoxic activities, thus contributing for anti-tumor immune suppression (Chen et al., 2005; Ghiringhelli et al., 2005; Strauss et al., 2007). Recent studies have shown that Tregs are implicated in inducing tumor progression (Kim et al., 2012; Merlo et al., 2009; Whiteside, 2014; Yamaguchi and Sakaguchi, 2006; Zou, 2006). Tumor antigens are recognized by autologous T cells (Pardoll, 2003)

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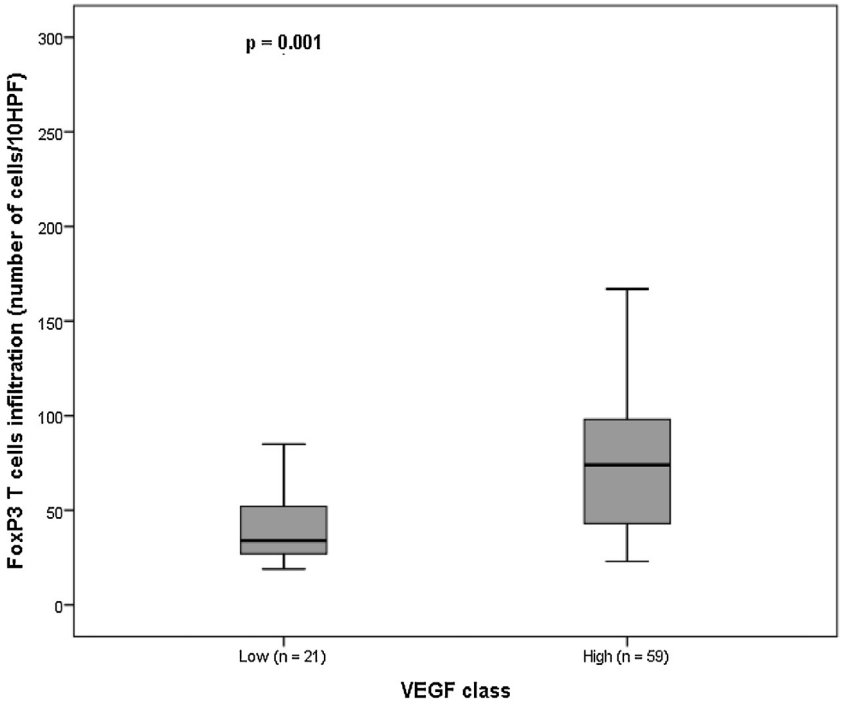

Fig. 1. FoxP3T cells distributed according to the VEGF class low or high and respective value of statistical significance for the ANOVA test.

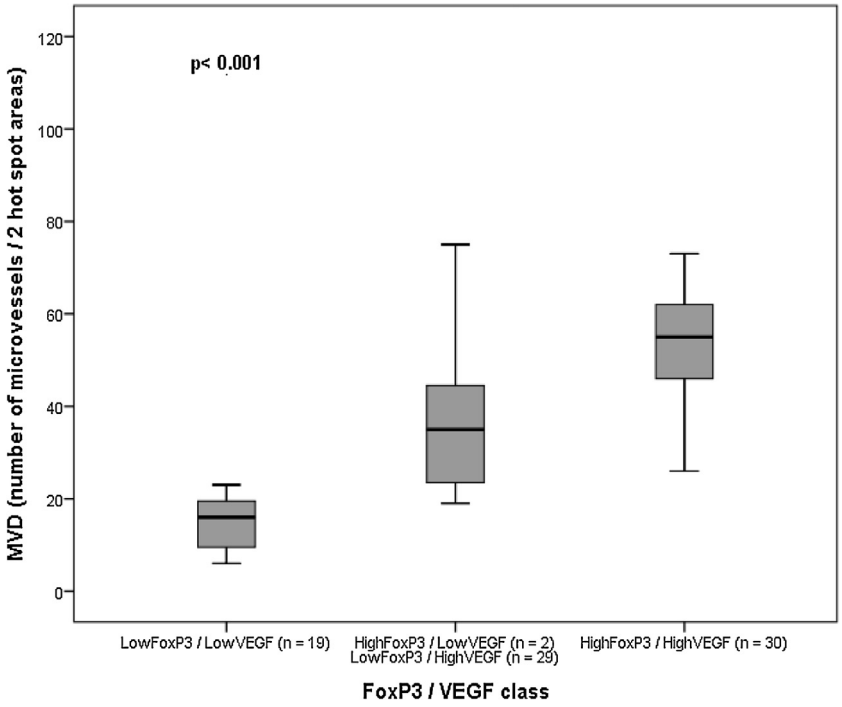

Fig. 2. Association of MVD (number of microvessels) distributed according to the FoxP3/VEGF class and respective value of statistical significance for the ANOVA test.

and are regarded as self by Tregs that actively promote their tolerance (Cao, 2010).

In human studies increased numbers of Treg cells have been associated with tumor aggressiveness and poor survival in many solid tumors, (Griffiths et al., 2007; Wolf et al., 2003) including breast cancer (Bates et al., 2006; Gao et al., 2015; Zhu et al., 2015). However, in breast tumors some groups have showed the association of Treg cells with good clinical outcome, (Zhang et al., 2015) highlighting the complexity of Tregs as a biomarker.

In dogs augmented Treg frequencies have been linked to tumor stage, prognosis and survival in several tumor types (Biller et al., 2007; Biller et al., 2010; Horiuchi et al., 2010; O'Neill et al., 2009; Tominaga et al., 2010). In turn, in classical and spermatocytic canine seminomas Foxp3Treg cells may be associated with a less malignant histological phenotype (Kim et al., 2013). In the context of canine mammary tumors (CMT), the importance of Tregs lies in the fact that increased numbers may favor tumor development or growth and influence the course of the disease, (Kim et al., 2012;

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