Immune Response in Nervous-Tissue Tumours: Immunohistochemical Study of Regulatory T Cells in Canine Glioma

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Introduction

Regulatory T cells (Treg), are under investigation for their proposed roles in suppressing tumour-specific immune responses and establishing an immunosuppressive tumour microenvironment, thus enabling to evade immune responses. Understanding Treg biology and mechanisms in the setting of cancer, and specifically the tumour microenvironment, is important for designing effective cancer immunotherapies.

Objectives

- Identification of molecular characteristics, biological rol, mechanisms of action and prognostic factors of regulatory T cells.
- Immunohistochemical analysis of regulatory T cells using molecular marker Foxp3⁺.
- Identification of Foxp3⁺ regulatory T lymphocytes in nervous-tissue and canine glioma.

Regulatory T cells

Development

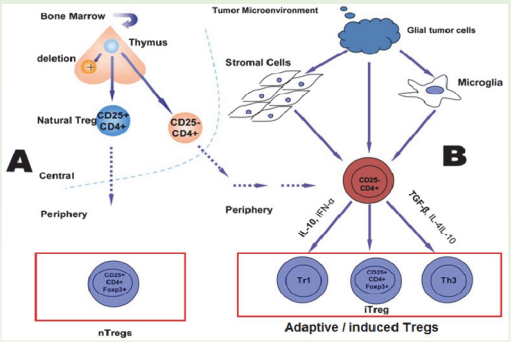

***Figure 1**. Development of Foxp3⁺ regulatory T cells (Humphries et al., 2010)*

Phenotypic markers

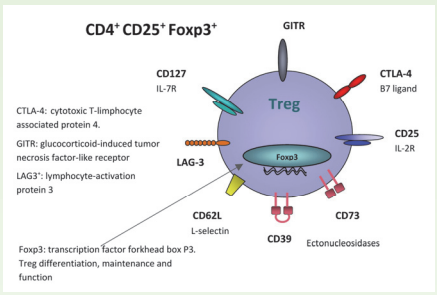

***Figure 2.** Phenotypic markers of Foxp3⁺ regulatory T cells*

Mechanisms and function

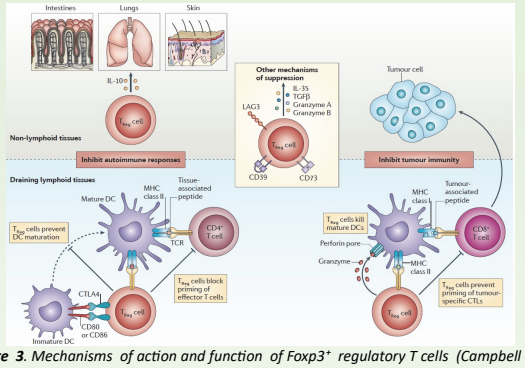

***Figure 3**. Mechanisms of action and function of Foxp3⁺ regulatory T cells (Campbell and Koch 2011)*

Function: establishing chronic infection

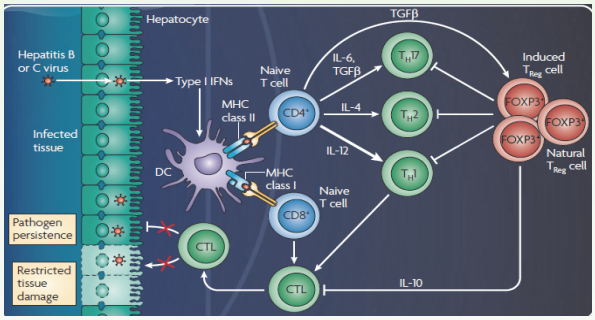

***Figure 4.** Function of Foxp3⁺ regulatory T cells in tissues. During infection Treg cells preventing immunity leading to the inability to clear the pathogen (Shevach and Davidson, 2010).*

Function: promoting tumour progression

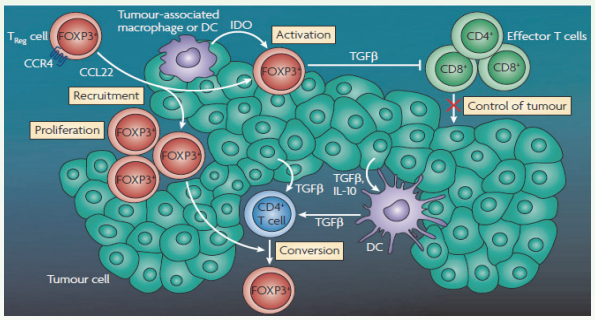

***Figure 5**. Accumulation of Foxp3⁺ regulatory T cells in tumour (Shevach and Davidson, 2010).*

Materials, methods and results

Table 1. Foxp3⁺ cell expression with histopathological and immunohistochemical features in canine gliomas

Histological type	*Foxp3⁺ cells*	**Lymphocytes (%)*	**Tumour cells (%)*	*Immunostaining intensity*	*Localization compartment*
oligodendrogliomas					
O	0/3				
AO	2/5				
AO *(case 1)*		0.5	0	H	Adjacent tumour
AO *(case 2)*		1-2	0	H	Adjacent tumour
astrocytomas					
AA	1/1				
AA *(case 1)*		6	0	I	Intratumoral
GBM	4/10				
GBM *(case 1)*		3	0	I, H	Intratumoral
GBM *(case 2)*		4-5	0	I, H	Adjacent tumour
GBM *(case 3)*		14	1	I, H	Intratumoral
GBM *(case 4)*		12.5	4	I, H	Intratumoral

**Only nuclear staining was considered positive.*

Abbreviations: O, oligodendroglioma; AO, anaplastic oligodendroglioma; AA, anaplastic astrocytoma; GBM, glioblastoma; H, high; I, intermediate; L, low.

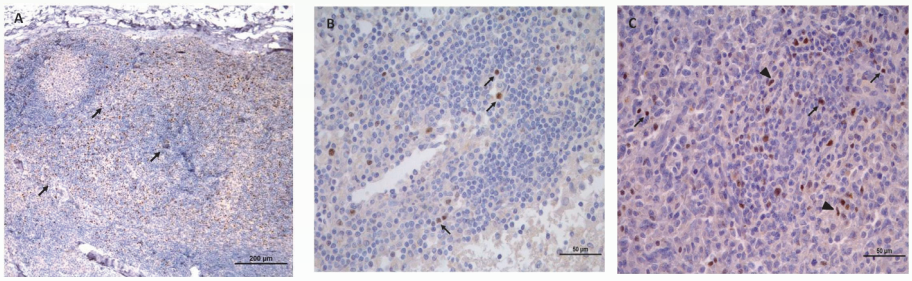

***Figure 6. A:** Foxp3 cells in lymph node. **B:** Foxp3⁺ cells in anaplastic astrocytoma. **C:** Foxp3⁺ cells in glioblastoma. Tumour cells (►), lymphocytes (→)*

Conclusions

This is the first study that evaluates the expression of Foxp3⁺ in canine gliomas by immunohistochemistry. The low number of gliomas evaluated does not allow definitive conclusions to be drawn, but our results suggest that:

- Foxp3⁺ is more frequently expressed in high-grade gliomas and correlates with the degree of tumour malignancy.
- The Foxp3⁺ expression is very similar to its human counterpart.
- The canine model could be used for the preclinical evaluation of treatment strategies, such us immunotherapy.

References

- Campbell, D.J. & Koch, M.A., 2011. Phenotypical and functional specialization of FOXP3+ regulatory T cells. *Nature reviews. Immunology*, 11(2), pp.119-30.
- Ethan Shevach and Todd Davidson, 2010. Regulatory T cells. *Nature reviews. Immunology.* Available at: http://www.nature.com/nri/posters/tregcells
- Humphries, W. et al., 2010. The Role of Tregs in Glioma-Mediated Immunosuppression: Potential Target for Intervention. *Neurosurgery Clinics of North America*, 21(1), pp.125-137.