The extracellular matrix (ECM) in canine gliomas: the role of the elements of the ECM in the persistence and invasiveness of canine gliomas

Sílvia Domingo Curto

Universitat Autònoma de Barcelona

Introduction

The study of the extracellular matrix (ECM) in the nervous tissue is at a very early stage. Recently, some works have appeared connecting ECM and gliomas to detect diagnostic, prognostic and therapeutic tools being effective in neuroncology. Different groups raise the utility dog and canine glioma as a animal model for the study of human gliomas.

Extracellular Matrix in the nervous tissue

ECM presents an heterogeneous organization, which found scattered among neuroglia or forming aggregates called perineuronal nets (**PNNs**) (figs 1, 2). The ECM represents a key environment for supporting the regenerative response of the nervous system, but also opposed to its change and participating in diseases, for example in helping the migration of neoplastic cells.

Each of its components performs different interactions, which determine their functions. The predominant elements are **proteoglycans** (**PGs**), **glycoproteins**, **glycosaminoglycans** (**GAGs**) and **hyaluronic acid** (**HA**).
Other outstanding molecules that take part of the basement membrane are **laminin**, **fibronectin** and **collagen IV**. Regarding the structure of the ECM, changes depending on the age of the animal, vary the expression of their components.

Glioma

Glioma is a type of tumor that originates in the CNS cells from glia. The incidence of primary tumors on nerve tissue in the dog reaches 1.9%. The main feature is the ability to propagate infiltrating normal nervous tissue.

Animal models for the study of gliomas

Till today, several animal models have been used, being rat and mouse the most used. However, they require translational studies and preclinical trials using other animal species closest to humans. Some of the reasons are the lack of spontaneous gliomas, variations in cytological and immunological murine nervous tissue, etc.. Instead **the dog** shows a great histological similarity with humans, it presents spontaneous gliomas and it is much closer to humans immunological, physiological and biochemically (figs 3a, 3b). Many veterinary neuropathologists use the classification of World Health Organization (WHO) for human glial tumors in 2007, since the last classification of gliomas canines date 2002.

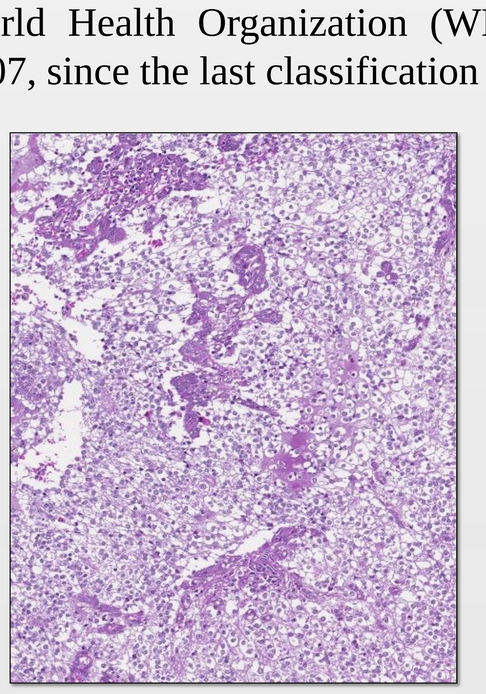

Fig. 3a. Glioblastoma in a dog. Glomeruloides vascular proliferation typical of this type of tumor (HE, x17).

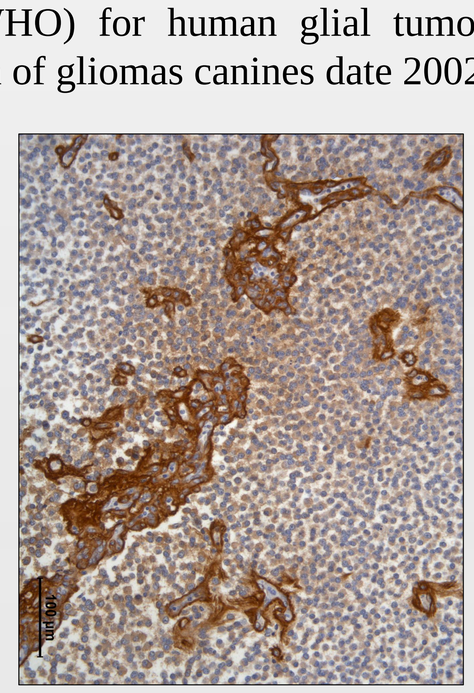

Fig. 3b. Glioblastoma in a dog. ECM basal lamina of glomeruloides vessels (IHC, Laminin, x30).

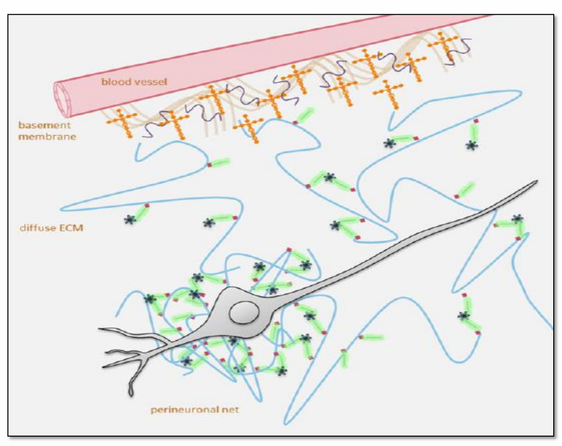

Fig. 1. Structure and ECM components. There is a diffuse interstitial matrix and condensed structures forming perineuronal networks, which surround the cell soma.

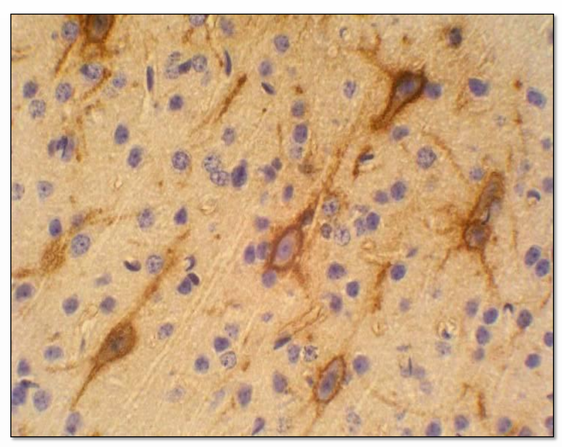

Fig. 2 ECM surrounding neurons in the frontal cortex (PNNs). Mouse. By lectin histochemistry technique (Wisteria floribunda, x40).

Gliomas and ECM

The ECM components that are more important in the ability of glioma invasion are **PGs**, specially heparan sulfates (**HSs**) and chondroitin sulfates (**CSs**); **HA**; **fibrillar proteins**; surface proteins such as **CD133** and **tenascin-C (TNC)**; **proteases**; highlighting glycoprotein **CD44** and E-Cadherin (**E-CAD**). Cancer cells have self-renewal capacity and properties of stem cells that produce abnormal elements of ECM or modifying it.

Recent evidencies :

- HSs: regulate the fibroblast (FGF), platelet derived (PDGF) and vascular endothelial (VEGF) growth factors. They produce interactions between ECM and cells, and cells to cells, providing cell mobility.
- HA: favor tumor growth causing areas in the tumor where to migrate and interact with other molecules.
- Interesting markers expressed in gliomas: HA, TNC, E-CAD and CD44.
- Proteases: drive propagation and direction of growth of gliomas. The most important are the metalloproteases.
- Integrin + laminin: guaranteeing the maintenance of tumor, and protecting tumor cells from radiation.

Conclusions

There are many projects studying the ECM components and their interaction with cells of gliomas, however, there are still many points to define and know about the role of each of them. The ultimate target is to identify elements that can be used as diagnostic and therapeutic tools. Displayed that the dog is an interesting model for its proximity to humans, which is already providing notable results, the study of the ECM in its nervous tissue is becoming an essential work to be done.