The role of angiogenesis in the invasiveness of canine gliomas

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Abstract

Gliomas are tumors that originate in the central nervous system from glial cells, being glioblastoma the most aggressive tumor, which is characterized by rapid and infiltrative growth, along with a poor prognosis owing to poor response to treatment. Glioblastoma is distinguished also by an abundant and aberrant vasculature, due to the tumor's ability to induce the formation of new vessels by mechanisms that mimic physiological angiogenesis. Knowledge of these processes, as well as molecules and cells involved, is useful for the discover of new therapeutic targets. In addition, the similarities observed between human and canine gliomas places this species as an ideal model for the study of gliomas.

Gliomas

- 81% of malignant primary brain tumors.
- More frequent in men than women and risk increases with age.
- Classified by OMS by cell origin and degree of aggressiveness (I to IV).
- Some mutations have been found in tumor suppressor genes (NF-1, p53, Rb1 and PTEN) or in oncogenic signaling pathways (PI3K/AKT/mTOR and Ras-MAPK pathways and TKs receptors EGFR and PDGFR).
- There exist also mutations in specific genes of gliomas, such as the promoter gene of MGMT and IDH gene, which have prognostic value.
- Glioma stem cells (GSC) have been found and have a role in treatment resistance and neovascularization.

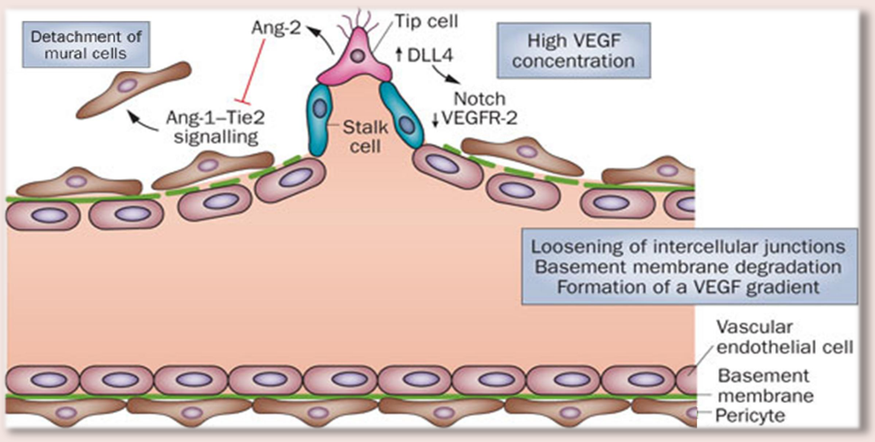
Canine Gliomas

- The incidence of intracranial tumors is 20/100.000.
- Meningioma is the most frequent (40%), followed by oligodendroglioma (20%) and astrocytoma (15%).
- Risk increases with age, with a mean age of 8,6 years old.
- Brachycephalic dogs have a major incidence, since the 50% of gliomas occurs in the Boxer, Boston Terrier and Bulldog breeds. This provides an ideal background to identify underlying genetic abnormalities.
- Mutations in P53 and EGFR have also been observed in canine gliomas, as well as the presence of GSC.
- There is a great similarity between canine and human gliomas in terms of imaging and histopathological features, as well as in the rapid evolution of the tumor.

Physiological angiogenesis

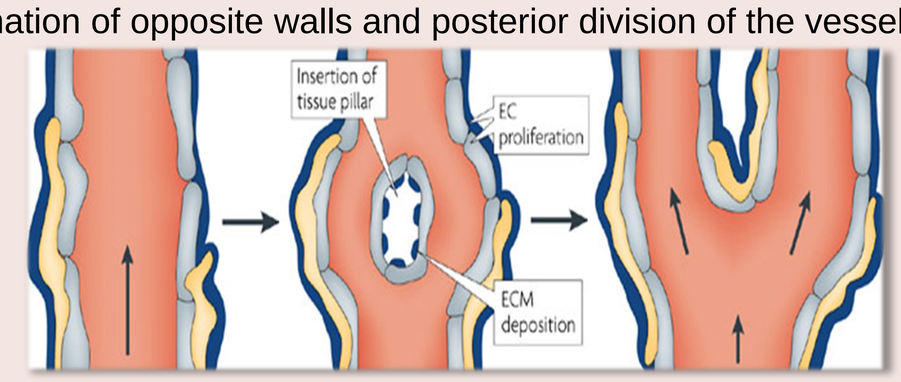
1. Sprouting Angiogenesis

An hypoxic or inflammatory signal promotes the expression of angiogenic factors (VEGF, Ang-1/2, FGFs…). Pericytes detach from the vascular wall and basal membrane, and the vascular permeability increases. VEGF helps along the differentiation of endothelial cells in a tip cell (which guides the new vessel) and stalk cells (in charge of replicating and making the vessel grow).



2. Intussusceptive Angiogenesis

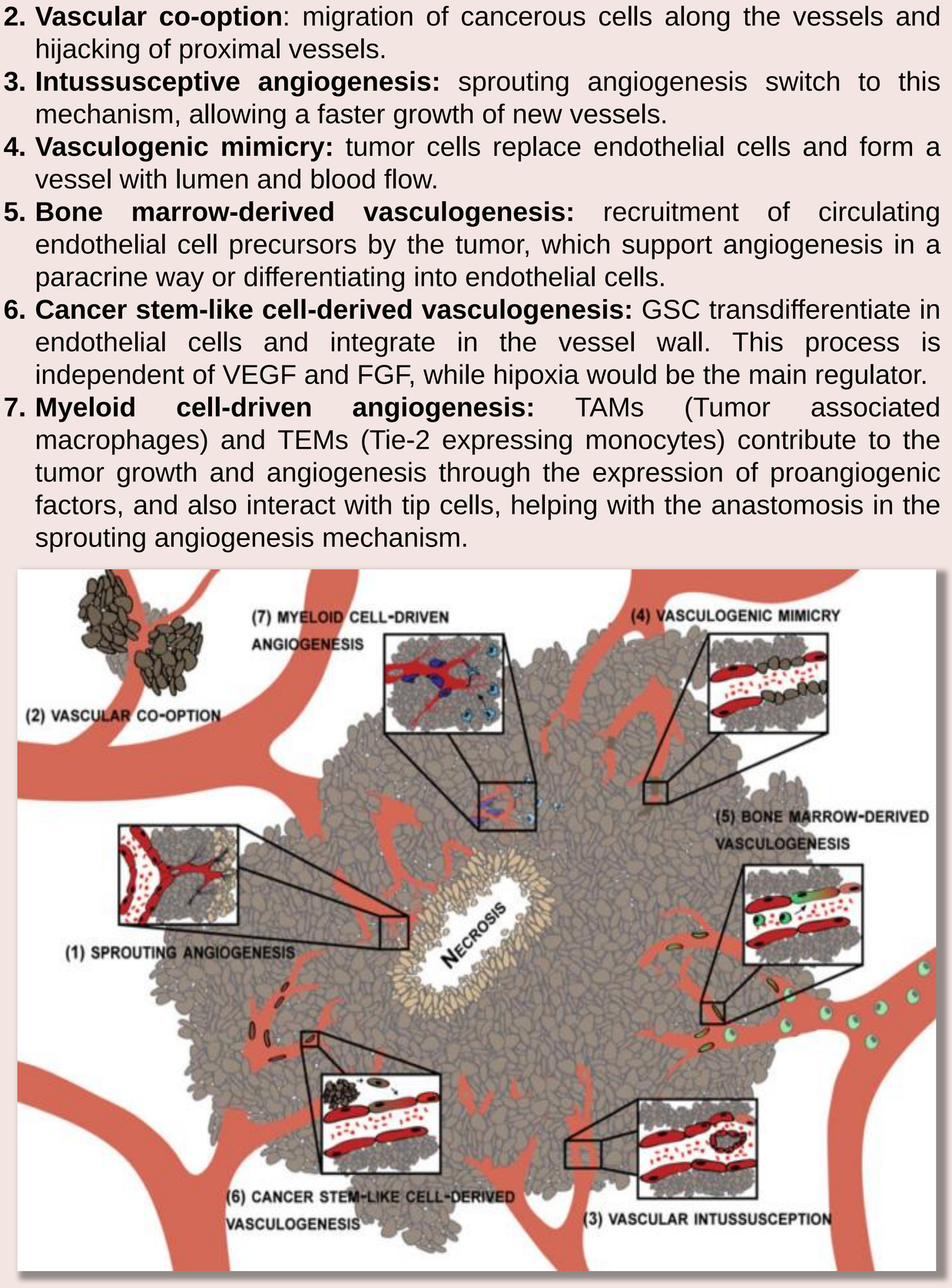
Formation of new vessels through the creation of an intraluminal pillar by invagination of opposite walls and posterior division of the vessel.



Glioma-derived angiogenesis

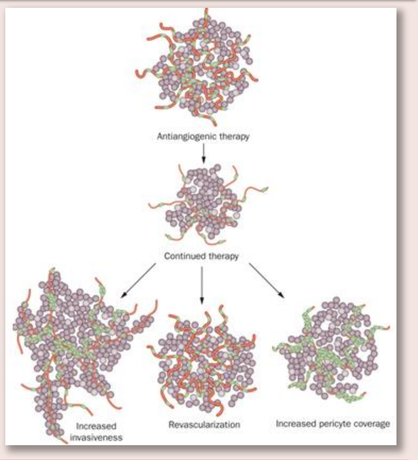
In order to survive, tumor cells are capable to induce the formation of new vessels through several mechanisms, which are:

1. **Sprouting angiogenesis:** it has an important role in glioma angiogenesis.
2. **Vascular co-option**: migration of cancerous cells along the vessels and hijacking of proximal vessels.
3. **Intussusceptive angiogenesis:** sprouting angiogenesis switch to this mechanism, allowing a faster growth of new vessels.
4. **Vasculogenic mimicry:** tumor cells replace endothelial cells and form a vessel with lumen and blood flow.
5. **Bone marrow-derived vasculogenesis:** recruitment of circulating endothelial cell precursors by the tumor, which support angiogenesis in a paracrine way or differentiating into endothelial cells.
6. **Cancer stem-like cell-derived vasculogenesis:** GSC transdifferentiate in endothelial cells and integrate in the vessel wall. This process is independent of VEGF and FGF, while hipoxia would be the main regulator.
7. **Myeloid cell-driven angiogenesis:** TAMs (Tumor associated macrophages) and TEMs (Tie-2 expressing monocytes) contribute to the tumor growth and angiogenesis through the expression of proangiogenic factors, and also interact with tip cells, helping with the anastomosis in the sprouting angiogenesis mechanism.



Therapies

Bevazicumab® is a monoclonal antibody against the VEGF factor, thus preventing the binding with their receptor and inhibiting angiogenesis.
Nevertheless, resistance mechanisms have been observed, such as overexpression of other pro-angiogenic factors (FGF, Ang-1…), increased recruitment of bone marrow cells, invasiveness via vascular cooption or covering by pericytes.



Conclusions

- Angiogenesis is a crucial process to survival and invasiveness of gliomas and contributes in the resistance mechanisms against existing treatments.
- Mechanisms of angiogenesis in gliomas are varied and complex, and they interact with each other.
- Understanding the mechanisms of angiogenesis that exist within the tumor will ease the development of new targeted therapies.
- Similarities existing between human and canine gliomas make this species an ideal model for the study of gliomas. Nevertheless, the mechanisms of angiogenesis involved in gliomas have not been studied in the canine species yet.