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Researchers describe a new target for developing anti-angiogenic and anti-tumoral therapies

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Researchers from the Spanish National Cancer Research Centre (CNIO), led by Jorge L. Martínez-Torrecuadrada from the Proteomics Unit, have demonstrated that the antibody-based blocking of ephrinB2, a protein involved in angiogenesis and lymphoangiogenesis, may represent an effective strategy for the development of antiangiogenic and antitumoural therapies.

The results of this study appeared in this month's issue of *Blood*, the journal of the American Society of Hematology.

CNIO researchers generated highly-specific human antibodies against ephrin-B2 using a phage display approach. These specific antibodies were able to suppress endothelial cell migration and tube formation in in vitro assays. Also, systemic treatment of mice xenografted with pancreatic, lung or colon carcinoma cells resulted in a significant reduction in the amount of blood and lymphatic vessels.

Concomitantly, a drastic inhibition of the tumour growth was observed in every xenograft mouse model used. Therefore, these results validated ephrinB2 as a potential therapeutic target in tumour angiogenesis and lymphangiogenesis and showed that the ephrinB2-specific antibodies developed in this study may be suitable as leads for the development of new improved antiangiogenic therapies, which can be used alone or can complement or synergise with other established antiangiogenic therapies

of application in cancer or other angiogenesis-related pathologies.

The angiogenesis process

Angiogenesis is a complex process by which new blood vascular vessels arise from pre-existing ones. In adulthood and under physiological conditions, this process only occurs in some circumstances, such as wound healing or in the menstrual cycle, but it is also an important factor in several pathologies such as cancer, in which the tumour promotes the formation of new blood vessels. This new vasculature provides the tumour with oxygen and nutrients, allowing these cells to grow, invade nearby tissue and eventually metastasise to distant organs.

In addition to blood vasculature, tumour growth induces the development of lymphatic vessels in a similar process called lymphangiogenesis that plays a key role in tissue–fluid homeostasis, as a tissue-drainage system. Recent studies also demonstrated the critical importance of this lymphatic vasculature for the metastatic spread of tumour cells.

In the last decades, the extensive research in the field of tumour-derived angiogenesis led to the identification of several angiogenic targets that can be effectively blocked in order to prevent the formation of new blood vessels in tumours, starving them of oxygen and nutrients and thereby preventing their growth.

As a result of these researches, several antibodies have been successfully developed and have demonstrated clinical utility in treating several tumour types, such as bevacizumab (Avastin®), which is based on the inhibition of vascular endothelial growth factor (VEGF) that promotes endothelial cell proliferation, migration and differentiation.

However, recent emerging experimental and clinical evidence suggests that tumours treated with this antiangiogenic strategy may eventually

develop resistance to therapy and exhibit a progression to greater invasiveness. Therefore, there is a pressing need to explore other angiogenic targets that can be used therapeutically, such as the one validated by CNIO researchers in the study now published in Blood.

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