PROJECT 1

DoS: Prof. Angelo Corti

Title: **Role of chromogranin A fragmentation in neuroendocrine tumor angiogenesis and its relationship with genomic profile and proteolytic machinery**

Curriculum: Experimental and Clinical Medicine

Project description

Chromogranin A (CgA) is an important regulator of tumor vascular physiology. Abnormal circulating levels of CgA have been detected in patients with neuroendocrine tumors (NETs) as NETs can secrete CgA.
Considering the role of CgA in angiogenesis, a question that remains to be answered is whether this protein has an effect on the regulation of tumor vascular biology and progression in NETs.
We have shown that full-length CgA_{1-439} and its N-terminal fragment CgA_{1-78} (vasostatin-1) inhibit VEGF-induced endothelial permeability, protect the endothelial barrier from the disassembly of endothelial-cadherin adherence junctions, gap formation, and vascular leakage induced by TNF, and reduce the traffic of tumor cells through the endothelial barrier. CgA also inhibits the transport of chemotherapeutic drugs in tumor tissues induced by NGR-TNF. In a study we have shown that CgA_{1-439} and the N-terminal fragment CgA1-76 inhibit angiogenesis, whereas the fragment CgA_{1-373} stimulates it. Interestingly, the $R_{373-R374}$ dibasic site of CgA is cleaved by thrombin and plasmin, suggesting that these proteases may have a role in tipping the CgA-angiogenic balance toward a pro-angiogenic state. The ratio of cleaved/total CgA is a predictor of poor outcome in patients with several malignancies.
We have also shown that solid tumors genetically engineered to release full-length CgA in their microenvironment have a reduced tumorigenicity and that administration of exogenous full-length CgA reduces tumor growth. However, we observed that the fragment CgA_{1-373} can promote tumor growth. We also observed that the structure of vessels is altered in NET G2 and G3, the more aggressive type of NET. These findings suggest that the abnormal production and fragmentation of CgA in NETs might contribute to regulate tumor growth, depending on the amount of the CgA produced and released, and on the different proteolytic machinery activated.

The aims of the project are a) to characterize proteolytic fragments of CgA in NETs, b) to evaluate their role in angiogenesis, and c) to assess their value as prognostic markers and therapeutic targets and their relationship with the genomic profile, proteolytic machinery and CgA gene polymorphism. In particular, the study will aim at investigating the extent of CgA cleavage in NET tissues and in circulation. The correlation of fragmented CgA with microvascular density and vascular structure, the prognostic value of CgA fragmentation, and the association of CgA genetic polymorphisms and mutation profile in cancer cells with tumor behavior will be analyzed. Finally, the impact of CgA fragmentation on angiogenesis and vascular function in NETs will be investigated using in vitro and in vivo models.

References (max. 3)

Helle KB, Corti A. Chromogranin a: A paradoxical player in angiogenesis and vascular biology. Cell. Mol. Life Sci. 2014

Crippa L, Bianco M, Colombo B, Gasparri AM, Ferrero E, Loh YP, Curnis F, Corti A. A new chromogranin a-dependent angiogenic switch activated by thrombin. Blood. 2013;121:392-402

Dondossola E, Crippa L, Colombo B, Ferrero E, Corti A. Chromogranin a regulates tumor self-seeding and dissemination. Cancer Res. 2012;72:449-459