Identification of a new vascular marker correlating with colorectal cancer metastatization to distant organ

A. Bertocchi\textsuperscript{1*}, S. Carloni\textsuperscript{1}, P.S. Ravenda\textsuperscript{2}, G. Bertalot\textsuperscript{3}, I. Spadoni\textsuperscript{1}, A. Lo cascio\textsuperscript{1}, S. Gandini\textsuperscript{3}, M. Lizio\textsuperscript{1}, C. Klaver\textsuperscript{4}, A. Maroli\textsuperscript{5}, P. Spaggiari\textsuperscript{2}, M. G. Jodice\textsuperscript{3}, C. Luise\textsuperscript{3}, M. Erreni\textsuperscript{6}, S. Pece\textsuperscript{3}, P. P. Di Fiore\textsuperscript{3}, G. Viale\textsuperscript{3}, A. Spinelli\textsuperscript{5}, C. Pozzi\textsuperscript{1}, G. Penna\textsuperscript{1}, M. Rescigno\textsuperscript{1}.

\textsuperscript{1}Humanitas Research, Department of mucosal immunology and microbiota, Milan, Italy.
\textsuperscript{2}European Institute of Oncology IEO, Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, Milan, Italy.
\textsuperscript{3}European Institute of Oncology IEO, Molmed, Milan, Italy.
\textsuperscript{4}European Institute of Oncology IEO, Molecular and Pharmaco-Epidemiology Unit, Milan, Italy.
\textsuperscript{5}Humanitas Research, Department of Pathology- Cancer Center, Milan, Italy.
\textsuperscript{6}Unit of Advance Optical Microscopy, Humaitas Clinical and research Center- IRCCS

*(lead presenter) e mail address: alice.bertocchi@humanitasresearch.it

Keywords (maximum 8): Colorectal cancer, gut vascular barrier, distant metastases, microbiota.

Distant metastases are the second leading cause of colorectal cancer-related mortality. After surgical resection of the primary tumor, 40% of colorectal (CRC) patients develop distant metastases in five years. Spreading of neoplastic cells from the primary tumor to regional lymph nodes (LN) is often associated with distant recurrence. However, several clinical trials have shown that lymphadenectomy is not reducing CRC recurrence. This phenomenon is probably due to a metastatic dissemination that occurs via the systemic blood circulation, rather than the lymphatic vessels. So far, it has not been fully described how such dissemination is achieved. We here hypothesized that the disruption of the vascular endothelium in colorectal tumor can be linked to cancer cell metastatization. We identified a new marker of permissive vasculature, which is more detectable in primary tumors of CRC patients that have developed distant metastases within five years. To better investigate vasculature disruption and its involvement in distant metastases formation, we looked at increased detection of this marker in a mouse model that develops spontaneous tumors mainly in the colon. These mice showed dismantled vasculature at the tumor level and they concomitantly exhibited the formation of a pre-metastatic niche at distant sites, which then favored the recruitment of metastatic cells. Understanding vasculature impairment mechanisms can shed light on the process of colon metastases and this marker can be used as a new prognostic biomarker to predict distant metastases formation.