

Anti-VEGF Treatment-Resistant Pancreatic Cancers Secrete Proinflammatory Factors That Contribute to Malignant Progression by Inducing an EMT Cell Phenotype

**Carmine Carbone¹, Geny Piro², Anna Tamburrino¹, Maria Mihaela Mina²,
Silvia Zanini², Giampaolo Tortora², Davide Melisi¹**

¹Digestive Molecular Clinical Oncology Research Unit, and ²Laboratory of Oncology and Molecular Therapy; Medical Oncology, "Azienda Ospedaliera Universitaria Integrata" and University of Verona. Verona, Italy

Context The resistance of tumors to antiangiogenic therapies is becoming increasingly relevant. There are currently no validated predictive biomarkers for selecting which cancer patients will benefit from antiangiogenic therapy. Also lacking are resistance biomarkers that can identify which escape pathways should be targeted after tumors develop resistance to VEGF treatment. Recent studies showed that anti-VEGF treatment can make tumor cells more aggressive and metastatic. However, the mechanisms and mediators of this are unidentified.

Objective We aimed this study at directly identifying the tumor cell-initiated mechanisms responsible for the resistance of pancreatic cancer to anti-VEGF treatment. **Methods** We established and validated two murine models of human pancreatic cancer resistant to the VEGF-specific antibody bevacizumab *in vivo*. We used a genome-wide analysis to directly identify which tumor-secreted factors were overexpressed by pancreatic

cancer cells that were resistant to anti-VEGF treatment. **Results** Rather than direct proangiogenic factors, we identified several proinflammatory factors that were expressed at higher levels in cells resistant to anti-VEGF treatment than in treatment-sensitive control cells. These proinflammatory factors acted in a paracrine manner to stimulate the recruitment of CD11b⁺ proangiogenic myeloid cells. Also, we found that secreted factors overexpressed by anti-VEGF treatment-resistant pancreatic cancer cells acted in an autocrine manner to induce epithelial-to-mesenchymal transition (EMT) and were thus responsible for increased aggressiveness of bevacizumab-resistant pancreatic tumors. **Conclusions** Our results identified proinflammatory factors and EMT markers as potential biomarkers for selecting patients with pancreatic cancer for antiangiogenic therapy.