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VEGF-induced intracellular Ca^2+ oscillations are weaker and do not stimulate proliferation in tumor-derived endothelial colony forming cells

Germano Guerra[1], Francesco Lodola[2], Umberto Laforenza[3], Fabio Cattaneo[4], Valentina Poletto[5], Estella Zuccolo[2], Marco Biggiogera[6], Vittorio Rosti[5], Domenico Tafuri[7], Francesco Moccia[2]

[1] Department of Medicine and Health Sciences "Vincenzo Tiberio", University of Molise, Via F. De Santis, 86100 Campobasso, Italy.
[2] Laboratory of General Physiology, Department of Biology and Biotechnology "Lazzaro Spallanzani", University of Pavia, 27100 Pavia, Italy;
[3] Department of Molecular Medicine, University of Pavia, 27100 Pavia, Italy;
[4] Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, 80131 Naples, Italy;
[5] Center for the Study of Myelofibrosis, Research Laboratory of Biotechnology, Foundation IRCCS Policlinico San Matteo, 27100 Pavia, Italy;
[6] Laboratory of Cell Biology and Neurobiology, Department of Biology and Biotechnology "Lazzaro Spallanzani", University of Pavia, 27100 Pavia, Italy;
[7] Department of Sport Sciences and Wellness, University of Naples "Parthenope", Naples, Italy.

Endothelial colony forming cells (ECFCs) represent a population of truly endothelial precursors that may be mobilized from their vascular stem cell niches to promote the angiogenic switch in a growing number of solid malignancies, including breast cancer (BC). While normal ECFCs require VEGF to proliferate, tumor-associated ECFCs are seemingly insensitive to this growth factor. This phenomenon could contribute to the relative failure of anti-VEGF therapies in cancer patients. Recent work showed that the intracellular Ca^2+ toolkit, which is a crucial determinant of ECFC fate and controls the pro-angiogenic program triggered by VEGF, is remodelled in tumor-associated ECFCs. Herein, we adopted an array of techniques, including Ca^2+ imaging, electron microscopy, flow cytometry, real-time polymerase chain reaction, western blot analysis and functional assay to investigate whether and how VEGF uses Ca^2+ signalling to control proliferation in BC-derived ECFCs (BC-ECFCs). Our results finally demonstrate for the first time that BC-ECFCs are insensitive to VEGF, which might explain at cellular and molecular level the failure of anti-VEGF therapies in BC patients, and hint at SOCE as a novel molecular target for this disease.

Keywords

VEGF, breast cancer, endothelial colony forming cells, intracellular Ca2+ oscillations, proliferation