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Title: The tyrosine-kinase inhibitor sunitinib targets vascular endothelial (VE)-cadherin: a marker of response to antitumoural treatment in metastatic renal cell carcinoma

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Abstract (300 word limit)

BACKGROUND: Vascular endothelial (VE)-cadherin is an endothelial cell-specific protein responsible for endothelium integrity. Its adhesive properties are regulated by post-translational processing, such as tyrosine phosphorylation at site Y685 in its cytoplasmic domain, and cleavage of its extracellular domain (sVE). In hormone-refractory metastatic breast cancer, we recently demonstrated that sVE levels correlate to poor survival. In the present study, we determine whether kidney cancer therapies had an effect on VE- cadherin structural modifications and their clinical interest to monitor patient outcome.

METHODS: The effects of kidney cancer biotherapies were tested on an endothelial monolayer model mimicking the endothelium lining blood vessels and on a homotypic and heterotypic 3D cell model mimicking tumour growth. sVE was quantified by ELISA in renal cell carcinoma patients initiating sunitinib (48 patients) or bevacizumab (83 patients) in the first-line metastatic setting (SUVEGIL and TORAVA trials).

RESULTS: Human VE-cadherin is a direct target for sunitinib which inhibits its VEGF-induced phosphorylation and cleavage on endothelial monolayer and endothelial cell migration in the 3D model. The tumour cell environment modulates VE-cadherin functions through MMPs and VEGF. We demonstrate the presence of soluble VE-cadherin in the sera of mRCC patients (n = 131) which level at baseline, is higher than in a healthy donor group (n = 96). Analysis of sVE level after 4 weeks of treatment showed that a decrease in sVE level discriminates the responders vs. non-responders to sunitinib, but not bevacizumab.

CONCLUSIONS: These data highlight the interest for the sVE bioassay in future follow-up of cancer patients treated with targeted therapies such as tyrosine-kinase inhibitors.

Image

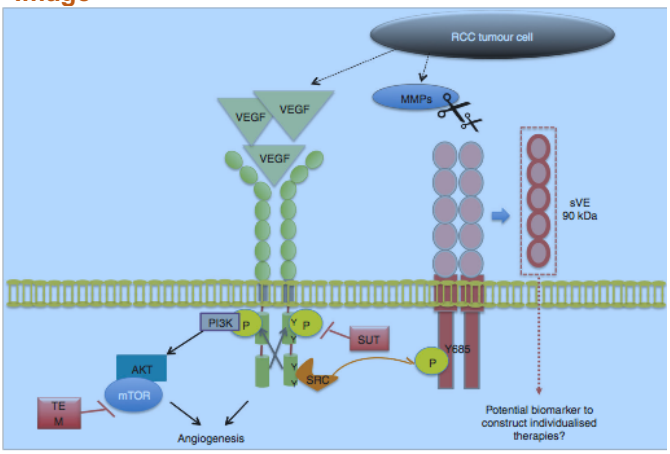


Fig. 1 : Proposed mechanisms of microenvironment-induced VE-cadherin structural modifications in kidney cancer. This working hypothesis was mainly built from our results obtained using in vitro EC cultures and VEGF as the major actor in angiogenesis.15, 20 The involvement of other cytokines in these processes cannot be excluded since we previously showed that TNFα induced sVE release19

Recent Publications

1: Polena H, Creuzet J, Dufies M, Sidibé A, Khalil-Mgharbel A, Salomon A, Deroux A, Quesada JL, Roelants C, Filhol O, Cochet C, Blanc E, Ferlay-Segura C, Borchiellini D, Ferrero JM, Escudier B, Négrier S, Pages G, Vilgrain I. *The tyrosine-kinase inhibitor sunitinib targets vascular endothelial (VE)-cadherin: a marker of response to antitumoural treatment in metastatic renal cell carcinoma.* Br J Cancer. 2018 May;118(9):1179-1188.

2: Rochefort P, Chabaud S, Pierga JY, Tredan O, Brain E, Bidard FC, Schiffler C, Polena H, Khalil-Mgharbel A, Vilgrain I, Bachelot T. Soluble *VE-cadherin in metastatic breast cancer: an independent prognostic factor for both progression-free survival and overall survival.* Br J Cancer. 2017 Jan;116(3):356-361.

3: Sidibé A, Polena H, Pernet-Gallay K, Razanajatovo J, Mannic T, Chaumontel N, Bama S, Maréchal I, Huber P, Gulino-Debrac D, Bouillet L, Vilgrain I. *VE-cadherin Y685F knock-in mouse is sensitive to vascular permeability in recurrent angiogenic organs.* Am J Physiol Heart Circ Physiol. 2014 Aug 1;307(3):H455-63.

4 : Vilgrain I, Sidibé A, Polena H, Cand F, Mannic T, Arboleas M, Boccard S, Baudet A, Gulino-Debrac D, Bouillet L, Quesada JL, Mendoza C, Lebas JF, Pelletier L, Berger F. *Evidence for post-translational processing of vascular endothelial (VE)-cadherin in brain tumors: towards a candidate biomarker.* PLoS One. 2013 Dec 16;8(12):e80056.

5 : Sidibé A, Polena H, Razanajatovo J, Mannic T, Chaumontel N, Bama S, Maréchal I, Huber P, Gulino-Debrac D, Bouillet L, Vilgrain I. *Dynamic phosphorylation of VE-cadherin Y685 throughout mouse estrous cycle in ovary and uterus.* Am J Physiol Heart Circ Physiol. 2014 Aug 1;307(3):H448-54.



Biography (150 word limit): **1980-1985 :** PhD Candidate, Biochemistry, Univ.Grenoble-Alpes, France. Thesis: Characterization of the Calcium activated, phospholipid dependent protein kinase

1985-1989 : CNRS Scientist Inserm Unit 244. Studied the role of proteine kinase C in the differentiated functions of adrenal gland

1989-1991 : Senior Research Associate at The Whittier Institute for Diabetes and Endocrinology, La Jolla, CA, USA. Mechanism of FGF-2 phosphorylation; Prof. Andrew Baird). Identified that FGF-2 must associate with its receptor to get be phosphorylated outside the cells by an ectoprotein kinase which regulates the activity and bioavailability of the growth factor.

1991-1999 : Cell signaling in adrenocortical cells

1999-2010 : Developed personal research program and interests in regulation and functions of VE-cadherin, identified one target site for VEGF dependent Src kinase phosphorylation of VE-cadherin, produced a knock'in mouse model (Y685F-VE- cad), developped a method to detect new biomarkers in medicine including soluble VE-cadherin.

2011-2015 : Developed personal research program on regulation and functions of VE-cadherin in cancer & vascular diseases such rheumatoid arthritis, hereditary angiodema, identified autoantibodies to VE-cadherin in dysimmune diseases.

2016-present : Team leader of Invasion Mechanisms in Angiogenesis and Cancer (IMAC) at Inserm U 1036

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