Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MASTER 2 RESEARCH SCHOLARSHIP - Program 2017 - 2018

INTERNSHIP PROPOSAL

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Research project title: How tumor cells talk to endothelial cells: a study in 2D and 3D cell culture models

5 Keywords to describe the project: *tyrosine kinases, phosphorylation, VE-cadherin, cross-talk, microenvironment*

Description of the project (aims, experimental techniques, recommended background):

Tumors are complex tissues that include various types of cells such as mesenchymal tumor cells, immune cells, and vascular endothelial cells. Therefore, the interaction between cancer cells and their microenvironment has been extensively studied. One major component of ECs, is VE-cadherin, an adhesive protein exclusively expressed in ECs and responsible for cell-cell cohesion and vascular integrity. In tumors, vascular beds are abnormal exhibiting leakiness and decreased blood flow. We have shown that VE-cadherin tyrosine phosphorylation at site Y685 and cleavage of its extracellular adhesive domain, is a specific signature of human tumor ECs. Very agressive breast tumor cell line are studied in the laboratory. There is overwhelming evidence that in vitro three-dimensional tumor cell cultures more accurately reflect the complex in vivo microenvironment than simple two-dimensional cell monolayers, not least with respect to gene expression profiles, signaling pathway activity and drug sensitivity. Understanding the mechanisms of endothelial cell and tumor cell interaction has been approached in vivo by tumor models in animals. In vitro, the two-dimensional (2D) cell culture model can be applied to a single cell type, whereas the three-dimensional (3D) model can allow co-culture of endothelial cells and tumor cells as well as Fibroblasts associated with tumors. The reconstruction of a 3D model is a challenge already well under way in recent years to study cell signaling and potential therapeutic strategies. The targeting of the tumor vascular network by the use of antiangiogenics is very promising even if mechanisms of resistance or escape to treatment are observed. The objective of this project and its originality is to optimize the development of 3D cell cultures integrating endothelial cells with tumor cells in order to better understand the signaling in the endothelial cell and the effect of anti-angiogenic therapies (neutralising antibodies and Inhibitors of tyrosine kinases). The analysis of the level of phosphorylation of VE-cadherin will be the readout of the study (based on the know-how existing in the laboratory), under the challenge of growth factors and inhibitors. The experimental conditions will be optimized to analyze the culture medium of these spheroids by antibodyarray to consider the discovery of new biomarkers before and after treatment with biotherapies including cleaved VE cadherin. Given the literature data showing that the signaling measured in 2D is different from that measured in 3D, this project may see the emergence of new concepts of the action of anti-angiogenic therapies

Methods: 2D & 3D cell culture, electrophoresis, westernblot, immunofluorescence

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Relevant publications of the team:

1-P Rochefort, S Chabaud, J-Y Pierga, O Tredan, E Brain, F-C Bidard, C Schiffler, H Polena, A Khalil-Mgharbel, I Vilgrain, T Bachelot. Soluble VE-cadherin in metastatic breast cancer: an independent prognostic factor for both Progression Free Survival and Overall Survival. British Journal of Cancer, accepted Dec 2016

2 : 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.

3- 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.