H.F.R.I.
Hellenic Foundation for Research & Innovation

Description of the funded research project

2nd Call for H.F.R.I. Research Projects to Support Post-Doctoral Researchers

Title of the research project: **Role of endothelial RhoA in cancer metastasis**

Principal Investigator: Constantinos Mikelis

Reader-friendly title: The role of RhoA in metastasis

Scientific Area: ΕΠ3 Life Sciences

Institution and Country: Texas Tech University Health Sciences Center, U.S.A.

Host Institution: University of Patras,

Collaborating Institution(s): N/A

Project webpage (if applicable): N/A

Budget: €180.000

Duration: 36 months

Research Project Synopsis

Metastasis, the leading cause of mortality in cancer patients, is the spread of cancer cells from the primary tumor to distant organs. During metastasis, cancer cells cross the monolayer of the endothelial cells, during entrance or exit from the vasculature. In many cancer types, permeability is increased in the metastasis-target organs prior to the arrival of the cancer cells. We therefore want to identify how cancer cells affect the endothelial monolayer in the metastasis-target organs, enabling metastasis. Based on our previous knowledge that the small GTPase RhoA in the endothelial cells regulates endothelial permeability, we propose that cancer cells activate RhoA in the endothelial cells, which augments their migration through the endothelium and enables metastasis. Therefore, we aim to: a) define the role of endothelial RhoA pathway on cancer cell trans-endothelial migration, by identifying the mechanism(s) and effect of RhoA blockade in vitro, using co-culture models, and in vivo, using tissue specific, conditionally-deficient mice and clinically relevant inhibitors; b) identify if the RhoA pathway is activated in the endothelium of the metastasis target organs. The transcriptomic and proteomic analysis of the targeted endothelial cells will reveal a potential role of endothelial RhoA on the early pre-metastatic events and will also identify other important vascular pre-metastatic mediators. The proposal aims to block cancer metastasis.

Project originality

For this project we are proposing a thorough analysis of the cancer-mediated stimuli that lead to RhoA activation in the endothelial cells. We propose paracrine mediators and cell-to-cell contact approaches the cancer cells employ for this activation, as well as the impact this has on endothelial cells in vitro and in vivo and to the metastatic potential. The generation of the endothelial-specific, tamoxifen-inducible RhoA-deficient mice is expected to provide reliable in vivo data. Finally, we propose to identify the impact of tumor-derived extracellular vesicles on endothelial RhoA activation via novel in vitro and in vivo approaches.

Expected results & Research Project Impact

To date, no pharmaceutical approaches against cancer metastasis exist. Based on our preliminary data, and should the rest of the experiments verify the hypothesis, blocking the endothelial RhoA pathway can provide an efficient anti-metastatic approach for a variety of cancer types.

The importance of this funding

This ambitious project would not be feasible without the H.F.R.I. funding. H.F.R.I. funding is the cornerstone for the development of my research program in Greece.

H.F.R.I.
Hellenic Foundation for Research & Innovation

H.F.R.I.
Hellenic Foundation for Research & Innovation

COMMUNICATION

185 Syggrou Ave. & 2 Sardeon St. 2
171 21, N. Smyrni, Greece
+30 210 64 12 410, 420
communication@elidek.gr
www.elidek.gr