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Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

Title of the research project: Investigation of the role of tumor suppressor CYLD in epithelial to mesenchymal transition

Principal Investigator: Georgios Mosialos

Reader-friendly title: Investigation of cancer metastatic mechanisms

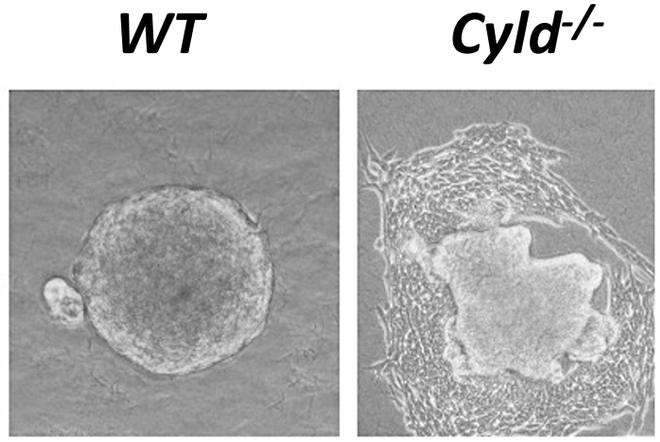
Scientific Area: Life Sciences-Medical and health sciences

Institution and Country: Aristotle University of Thessaloniki, Greece

Host Institution: School of Biology

Collaborating Institution(s): Hubrecht Institute

Project webpage (if applicable):



CYLD-deficient mammary epithelial cells (*Cyld*$^{-/-}$) with enhanced mesenchymal phenotype are highly invasive in the surrounding semisolid medium compared to their wild type (*WT*) counterparts.

G. Mosialos

Budget: 180000 €

Duration: 36 months

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Research Project Synopsis

Inactivation or downregulation of the tumor suppressor CYLD has been implicated in the development of breast cancer. The molecular mechanisms that are deregulated in mammary epithelial cells with CYLD deficiencies are largely unknown. The proposed project is based on solid preliminary data that we have obtained from studies in human mammary epithelial cells, which indicate a critical role for CYLD downregulation or inactivation in the induction of epithelial to mesenchymal transition (EMT). EMT is considered a critical process for the development of metastatic phenotype of various tumors. In addition, recent evidence supports the role of EMT in the development of cancer stem cell phenotype. Our preliminary data indicate that EMT induction by CYLD inactivation or downregulation in mammary epithelial cells is linked to the activation of TGFbeta pathway in a manner that does not depend on the activation of TGFbeta receptors. Interestingly, activation of TGFbeta has been linked to impaired DNA damage response. The mechanism of TGFbeta pathway regulation by CYLD and its possible implication in DNA damage response will be investigated in the context of the proposed project. Molecules that are regulated by CYLD in mammary epithelial cells will be identified and their role in EMT induction will be investigated. In addition, the susceptibility of CYLD-deficient mammary epithelial cells to DNA damage and relevant mechanisms will be investigated. The potential of CYLD to regulate EMT will be investigated in primary human organoids in order to investigate the broader biological significance of our findings. The proposed project will provide novel information on critical molecular mechanisms that underlie the development and progression of breast cancer.

Project originality

The project will investigate previously unexplored mechanisms of epithelial to mesenchymal transition (EMT) in breast cancer. Understanding EMT has the potential to revolutionize the treatment of cancer. The project involves state of the art approaches that include targeted proteomic methods to identify ubiquitinated proteins that are regulated by CYLD and the use of human mammary organoids to investigate the role of CYLD in mammary epithelium homeostasis. In addition, a systematic approach to investigate the involvement of CYLD in DNA repair mechanisms will be used. It should be noted that the systematic identification of ubiquitinated proteins that are targeted by CYLD will be attempted for the first time. Similarly, the proposed project will investigate for the first time the possible effect of CYLD in specific DNA repair mechanisms. Furthermore, the establishment and use of human mammary organoids for the analysis of the biological function of CYLD is a significant novel aspect of the proposed research that will provide highly relevant answers to the pathobiology of human mammary neoplasias.

Expected results & Research Project Impact

Breast cancer is the most common cancer in women worldwide and the second most common cancer overall (http://eco.iarc.fr/eucan/Default.aspx). It is the fifth most common cause of death from cancer in women. These facts highlight the enormous socioeconomic impact that the progress in understanding and treating breast cancer can have. The proposed project will make a major contribution in understanding the molecular mechanism that drives EMT, a critically important process for promoting metastasis and the cancer stem cell phenotype. Both hallmarks are tightly linked to the aggressiveness and lethality of breast cancer. Therefore, a significant advancement in our understanding of fundamental principles that underlie these phenotypic changes will lay the ground for improving prognostic protocols, tailoring therapies to individual patient's cancer profile and developing effective targeted therapies for breast cancer.

The importance of this funding

Funding sources to support fundamental research are extremely limited despite their paramount importance for generating new knowledge and promoting highly quality education and training. The H.F.R.I. funding provides absolutely necessary support to promote our fundamental research in highly significant biomedical problems. It will give us the opportunity to establish and use state of the art techniques in biomedical research that would not have been possible to introduce in our lab and institution at this time without this support. The H.F.R.I. funding will permit the training of young researchers and the collaboration with a top-level European biomedical research institution that will advance our know-how in cutting edge technologies and improve our competitiveness and possibilities to attract additional funding.

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