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Hellenic Foundation for Research & Innovation

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: **Robo4 as regulator and biomarker of obesity-related adipose tissue dysfunction and insulin resistance**

Principal Investigator: **Antonios Chatzigeorgiou (MD, PhD)**

Reader-friendly title: **Robo4 in obesity**

Scientific Area: **Life Sciences / Physiology, Pathophysiology and Endocrinology**

Institution and Country: **National and Kapodistrian University of Athens, Greece**

Host Institution: **National and Kapodistrian University of Athens, Greece**

Collaborating Institution(s): -

Budget: 178.470 Euro

Project webpage (if applicable): .

Duration: 3 years

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Research Project Synopsis

Obesity is major problem worldwide and is linked to the development of pathologies such as insulin resistance and atherosclerosis. The low-grade inflammatory state, present predominantly in the adipose tissue (AT) during obesity is considered a critical contributor for the development of metabolic dysregulation. In parallel, angiogenesis has emerged as cardinal regulator of healthy AT expansion, while blockage of angiogenesis in late-stage obesity leads to adipocyte apoptosis and has been proposed as an efficient way of reducing adiposity and improving glucose tolerance. Although the implication of endothelium in both inflammation and angiogenesis of metabolic organs is not only indisputable but also of considerable clinical interest, the exact mechanisms underlying the control of endothelial homeostasis of the obese AT remain largely unclear. Robo4, an endothelial-specific receptor, has been shown to govern endothelial permeability and angiogenesis in a way that interaction of Robo4 with its ligand Slit2 conduces to maintenance of vascular integrity. Nevertheless, its implication in obesity-related AT pathophysiology or its utility as therapeutic target or biomarker of AT condition and thus metabolic dysregulation is entirely unaddressed. The aim of the proposal is to determine in vivo and in vitro whether Robo4 is of major importance for AT pathophysiology and metabolic dysregulation by altering AT inflammation and angiogenesis or affecting pathophysiological features of other metabolically-relevant tissues.

Project originality

The major novel aspect of the current proposal is that we intend to determine the role of an endothelial-specific receptor, able to regulate multiple principal features of the pathophysiology of the endothelium such as inflammation, angiogenesis and vascular leakage, affecting finally metabolic dysregulation of overall the respective tissues. In addition, the current study, apart from highlighting the implication of an endothelial molecule in the development of obesity-related metabolic dysregulation, aims to reveal its importance as a biomarker of disease or pathophysiological features of the implicated tissues in humans. The proposal capitalizes on the strong experience of the applicant in basic research methods including both in vivo and in vitro approaches as well as preclinical translational animal models (mice) and valuable human samples, providing thus a comprehensive research package to address the objectives of the project .

Expected results & Research Project Impact

So far, emerging evidence is pointing towards a major role of obesity-associated hyperlipidemia, hyperglycemia and other metabolic stresses in endothelial dysfunction; nevertheless the exact mechanisms of how the endothelium regulates metabolic homeostasis remain largely unexplored to date. By dissecting the role of an endothelium-specific receptor, the signalling of which affects multiple processes such as endothelial permeability and inflammation in the context of obesity, the applicant brings to the forefront a totally novel question in the field of obesity-related dysregulation of metabolic organs. Notably, for the execution of the current proposal, the applicant is using a knockout mouse strain that is not commercially available. In addition, apart from generating novel pathophysiological knowledge, the present proposal will propose innovative therapeutic approaches to prevent adipose tissue dysfunction and insulin resistance so far not harnessed by current antidiabetic drugs. Besides, taking into account that several of the accompanying complications of obesity, such as atherosclerosis and diabetic angiopathy are endothelium-dependent and endothelium-oriented, analyzing such an important endothelial receptor will likely have beneficial effects not only against insulin resistance itself but also against other obesity- or endothelium-related pathologies. The latter may pave the way for further experimental hypotheses and research proposals. In addition, taking into account the worldwide prevalence of obesity, the fulfilment of the current proposal will have an enormous impact on the society and economy, since the identification of novel diagnostic tools and therapeutic agents not only ensure a better quality of life for the patients but also unburden health systems.

The importance of this funding

Having recently started his own lab as an Assistant Professor of Physiology in Medical School of Athens, funding of the current proposal allowed the PI to establish and lead an independent research group in his new host Institution.

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