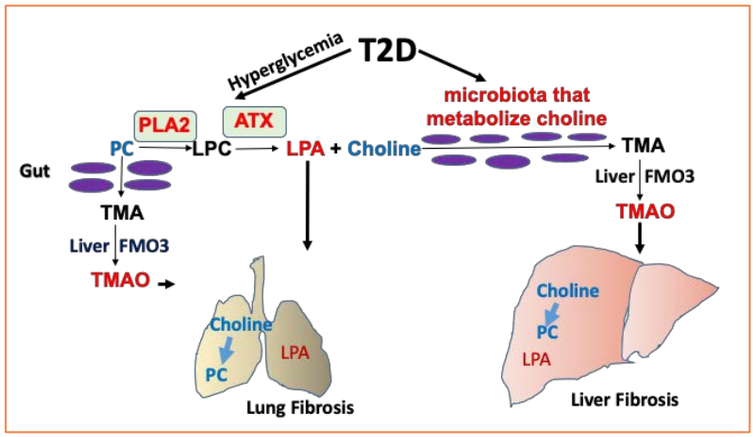
H.F.R.I.
Hellenic Foundation for Research & Innovation

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: Type 2 Diabetes drives pulmonary and liver fibrosis through phospholipid and microbiota metabolism



Principal Investigator: Eleanna Kaffe

Reader-friendly title: Type 2 Diabetes can contribute to pulmonary and liver fibrosis by altering the lipid metabolism and the microbiota

Scientific Area: Pathophysiology

Institution and Country: H.F.R.I, Greece

Host Institution: B.S.R.C Alexander Fleming

Collaborating Institution(s): Yale University

Project webpage (if applicable):

Budget:180.000

Duration: 3 years

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

Research Project Synopsis

Patients with fibrotic Non Alcoholic Fatty Liver Disease (NAFLD) or Idiopathic Pulmonary Fibrosis (IPF) have often Type 2 diabetes mellitus (T2DM). Recent epidemiological studies and systematic reviews clearly indicate that diabetes is an independent risk factor for pulmonary dysfunction in IPF patients and progressive liver disease. However, the mechanisms underlying these striking associations remain unknown. This is a very important question to be examined given that T2DM is a fast-growing epidemic in industrialized countries. Understanding how the metabolic remodeling occurring in diabetes may affect fibrosis initiation and progression will unveil novel preventive and therapeutic approaches that could decrease the risk of fibrosis or halt its progression to fatal end stage lung and liver disease. Here, we hypothesize that hyperglycemia of T2D confers an increased risk of progressive liver and lung fibrosis via alterations in phospholipid and microbiota metabolism. In particular, we will examine whether diabetes induced alterations in phospholipid metabolism and in specific microbiota are involved in the liver and lung fibrosis using animal models and mouse genetics. Our first goal is to examine which metabolic alterations of diabetes are responsible for driving liver and lung fibrosis. Our second goal is to address whether hyperglycemia through ATX/LPA/LPAR2 can drive liver and lung fibrosis and to investigate the role of deregulated PC levels in IPF animal models by modulating PC levels in vivo with genetic and dietary approaches. Our third goal is to investigate the role of microbiota metabolites such as Trimethyamine (TMA), found increased in patients with T2D, IPF and NAFLD, in animal models of IPF and NAFLD. At the end, we will validate our important findings in a humanized mouse system having human immune and stromal cells. These experiments will provide proof-of-principle for the role of deregulated lipids in lung and liver fibrosis.

Project originality

The present study has a significant potential to provide proof-of-concept for novel therapeutic targets. These targets include 1)LPAR2, a G protein-coupled receptor (GPCR), 2)TMA lyase, the bacterial enzyme converting choline into TMA, the precursor of TMAO and 3) Phospatidylcholine supplementation as a novel therapeutic intervention for IPF. Furthermore, our study also aims to establish innovative technologies for future drug discovery. The development of a novel humanized mouse model of NAFLD and IPF will be an important technological advancement. This model will be a unique tool to target human molecular targets in human hepatocytes or human immune cells and stromal cells in a pathophysiological context of NAFLD or IPF in vivo. This humanized system will be a valuable platform for the preclinical study of novel therapeutics.

Expected results & Research Project Impact

1.This study will shed light on how T2D increases the risk for fibrosis in NAFLD and IPF. Considering that T2D is fast growing pandemic, this association may explain the increasing incidence of HCC among NAFLD patients over the last years and the increase of IPF incidence, a fatal disease.

2. The ATX/LPA axis as a novel, druggable link between T2D and fibrosis. High ATX and LPA levels in patients with chronic liver disease associate with poor survival. However, the role of ATX/LPA signaling through LPARs in chronic liver diseases still remains totally unknown. One aim of our study is to addresses this important gap of knowledge. Notably, ATX inhibitors are currently being tested in clinical trials in humans with IPF. Thus, if this axis mediates the effect of T2D in the progression of NAFLD it can be translated soon in the clinic for NAFLD patients. To date, no evidence-based drug therapy has been approved for NAFLD management

3. The Choline/Microbiota/TMAO axis as a novel, druggable link between T2D and fibrosis. TMAO and the microbiota that hydrolyze choline to TMA were found increased in patients with T2D as well as in patients with NAFLD. Moreover, TMAO can exacerbate mortality in patients with pulmonary dysfunction, a primary characteristic of IPF patients. However, the role of TMAO in NASH and IPF remains totally unknown. This gap is addressed by our study. The inhibition of the bacterial enzyme that processes choline to TMA (TMA-lyase) is a promising and safe therapeutic strategy.

4. Humanized animal models of IPF and NAFLD are lacking and this is a big gap in the translation of findings from mice to humans. Our study will examine for the fist time human specific molecular targets in human cells within the pathophysiological context of liver and lung fibrosis *in vivo*.

The importance of this funding

The H.F.R.I. funding of my research will be very invaluable for the implantation of my research in Greece and for the transfer of humanized and *in vivo* metabolism technology to Greece. This funding will help in the discovery of novel therapeutic targets in fatal diseases that affect millions of people.

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