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NMRK2 kinase: a new target for a metabolic therapy of heart failure

Prof. Mathias Mericskay

Director of Research at INSERM

INSERM UMR 1180 Signalisation et Physiopathologie Cardiovasculaire

Faculté de Pharmacie, Université Paris-Sud

Paris, France

Heart failure is known to be associated with metabolic perturbations and energy deficit in the myocardium. Recently, we identified a deficit in myocardial NAD levels in the failing heart and pathological changes in the biosynthetic pathways for this major coenzyme used in energy metabolism but also by signaling pathways involved in redox and energy stress sensing such as the Sirtuins, the PARP1 enzyme or the CD38-mediated Ca2+ signals. This presentation will detail our most recent data on the role of an alternative NAD salvage pathway driven by the nicotinamide riboside kinase 2 (NMRK2) and how to target this pathway to restore NAD homeostasis in the failing heart.

SHORT BIOGRAPHY

EDUCATION

University Denis Diderot, Paris 7 – Master degree 1995

University Denis Diderot, Paris 7 – PhD degree 1999

Mount Sinai Hospital, NYU, USA – Postdoc 2003

University Pierre et Marie Curie,Paris 6 – HDR degree 2010

POSITIONS AND HONORS

1999 Louis Forest PhD Award of the Chancellery of the Universities in Paris

2000 Young Investigator Award from Fondation Bettencourt-Schueller

2003-2007 Investigator class 2 at INSERM, University Denis Diderot, Paris 7, France

2007-2016 Investigator class 1 at INSERM, University Pierre et Marie Curie, Paris 6

2011-2019 Election to the research board of the French Society of Cardiology

2016-2017 Investigator, class 1 at INSERM, University Paris-Sud, France

2018- Director of Research, class 2 at INSERM, University Paris-Sud, France

RESEARCH INTEREST

My team focuses on the molecular mechanisms involved in the structural and metabolic remodeling underlying the pathogenesis of heart failure. We studied the role of SRF (Serum Response Factor) as a key transcriptional regulator of cardiac genes that is repressed or activated in different models of cardiomyopathies and in human heart failure. Our results point to a central role of SRF in the coupling of structure and energy metabolism, a cornerstone for muscle tissues functions, that is altered in genetic diseases like dilated cardiomyopathy and during ageing. More recently we identified defects in NAD coenzyme metabolism in the failing heart of SRF cardiac specific KO mice and in human failing hearts. We found perturbation in the NAD biosynthetic pathways with a shift toward a new form of vitamin B3, the nicotinamide riboside as preferred energy-saving precursor. These pathways are linked to the sirtuins deacetylases and the AMPK pathways. Our ongoing research program aims to identify biomarkers of energy metabolism perturbation in heart failure and to develop metabolic therapies aiming at restoring energy balance in the failing heart notably through restoration of NAD pools.

PUBLICATIONS

Scopus H-index: 25, 46 publications (37 article, 9 reviews)

10 selected publications

1) Aged Nicotinamide Riboside Kinase 2 Deficient Mice Present an Altered Response to Endurance Exercise Training. Deloux R, et al. & Mericskay M. Front Physiol. 2018;9:1290.
2) Rescue of biosynthesis of nicotinamide adenine dinucleotide protects the heart in cardiomyopathy caused by lamin A/C gene mutation. Vignier N, et al. & Muchir A. Hum Mol Genet. 2018;27:3870-3880.
3) Nicotinamide Riboside Preserves Cardiac Function in a Mouse Model of Dilated Cardiomyopathy. Diguet N, Trammell SAJ, et al. & Brenner C, Mericskay M. Circulation. 2018;137:2256-2273.
4) Nicotinamide riboside, a form of vitamin B3, protects against excitotoxicity-induced axonal degeneration. Vaur P, Brugg B, Mericskay M, et al. & Duplus E. FASEB J. 2017;31:5440-5452.
5) Regulation of Connective Tissue Growth Factor and Cardiac Fibrosis by an SRF/MicroRNA-133a Axis. Angelini A, Li Z, Mericskay M*, Decaux JF*. PLoS One. 2015;10:e0139858.* corresponding authors.
6) Proteome modulation in H9c2 cardiac cells by microRNAs miR-378 and miR-378. Mallat Y, et al. & Mericskay M. Mol Cell Proteomics. 2014;13:18-29.
7) Inactivation of serum response factor contributes to decrease vascular muscular tone and arterial stiffness in mice. Galmiche G, Labat C, Mericskay M et al. & Li Z. Circ Res. 2013;112:1035-45.
8) Muscle creatine kinase deficiency triggers both actin depolymerization and desmin disorganization by advanced glycation end products in dilated cardiomyopathy. Diguet N, et al. & Mericskay M. J Biol Chem. 2011;286:35007-19.
9) Mosaic inactivation of the serum response factor gene in the myocardium induces focal lesions and heart failure. Gary-Bobo G, et al. & Mericskay M. Eur J Heart Fail. 2008;10:635-45.
10) Serum response factor is required for sprouting angiogenesis and vascular integrity. Franco CA, Mericskay M, et al. & Li Z. Dev Cell. 2008;1:448-61.