SingHealth DukeNUS ACADEMIC MEDICAL CENTRE
Institute of Biodiversity Medicine

National Cancer Centre Singapore
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BD-MED Nutrition Lecture Series

Multi-omics approaches define the roles of branched-chain amino acids in cardiometabolic diseases

Date: 19th January 2022 (Wednesday)
Time: 9:00 a.m. – 10:00 a.m.
Venue: Virtual Lecture *via* Zoom
Join Zoom Meeting:
https://nus-sg.zoom.us/j/82788673973?pwd=RVBVWnWpWyttaHBoM09aZkRDTDJzUT09
Meeting ID: 827 8867 3973
Passcode: 418549

Abstract:

We use *multi-omics* technologies to investigate metabolic regulatory mechanisms underlying development of cardiometabolic disease phenotypes. Our work has identified a *metabolomic* signature of perturbed branched chain amino acid (BCAA) catabolism that is associated with cardiometabolic diseases, predictive of intervention outcomes, and highly responsive to the most efficacious interventions for obesity and diabetes. BCAA restriction in Zucker fatty rats (ZFR) improves insulin sensitivity and lowers elevated triglyceride levels in heart via activation of fatty acid oxidation. Tissue metabolic profiling demonstrates that relief of mitochondrial fuel overload serves as a contributing mechanism for this effect. Metabolic flux analysis ("*fluxomics*") demonstrates dynamic reciprocal regulation of tissue glycine levels in response to changes in BCAA, serving to relieve muscle nitrogen burden and export incompletely oxidized acyl CoAs out of muscle tissue in the form of glycine adducts. We have studied the effects of small molecule inhibition of the kinase (BDK) or overexpression of the phosphatase (PPM1K) that regulate activity of the branched-chain ketoacid dehydrogenase (BCKDH) complex. Manipulation of BDK or PPM1K to activate BCKDH improves glucose, lipid and amino acid homeostasis in ZFR, including enhancement of insulin sensitivity and lowering of liver triglycerides. *Phosphoproteomic* analysis identified ATP-citrate lyase (ACL) as a novel BDK/PPM1K substrate, and overexpression of BDK is sufficient to phosphorylate and activate ACL, leading to increased hepatic *de novo* lipogenesis. Additionally, *transcriptomic* profiling reveals that BDK is upregulated and PPM1K downregulated by fructose feeding and the ChREBP-b transcription factor, identifying a ChREBP-regulated mechanism that links BCAA, glucose and lipid metabolism. Exposure of the heart to the levels of branched-chain keto acids (BCKA) found in obesity leads to phosphoproteome remodeling and activation of protein synthesis, possibly contributing to obesity-associated cardiac hypertrophy. Finally, *microbiome profiling* reveals that obese humans upregulate microbial BCAA biosynthesis genes and have increased microbial production of BCAA, possibly contributing to the expanded pool of BCAA and BCKA associated with cardiometabolic disease risk in obese subjects.

Our Speaker:



Dr. Christopher Newgard

Director, Sarah W. Stedman Nutrition and Metabolism Centre
Founding Director, Duke Molecular Physiology Institute
W. David and Sarah W. Stedman Distinguished Professor,
Duke University Medical Centre
Durham, NC USA

Christopher B. Newgard, Ph.D. is Director of the Sarah W. Stedman Nutrition and Metabolism Center, founding Director of the Duke Molecular Physiology Institute, and the W. David and Sarah W. Stedman Distinguished Professor at the Duke University Medical Center. Prior to coming to Duke in 2002, Dr. Newgard was the Gifford O. Touchstone Jr. and Randolph G. Touchstone Distinguished Professor, Department of Biochemistry, and Co-Director of the Touchstone Center for Diabetes Research, University of Texas Southwestern Medical Center, Dallas. Dr. Newgard's research applies interdisciplinary tools for understanding of cardiometabolic disease mechanisms including gene discovery, metabolic engineering, and comprehensive metabolic analysis. Dr. Newgard has authored 400 peer-reviewed and review articles (Clarivate h-index, 103), and has been the recipient of several awards, including the Outstanding Scientific Achievement (Lilly) Award from the American Diabetes Association (2001), a Merit Award from the NIH (2001), a Bristol Meyers-Squibb "Freedom to Discover" Award (2006), a Duke Medical Alumni Association Distinguished Professorship (2016), and an Outstanding Innovator Laureate Award from the Endocrine Society (2020).

Hosted by:
Professor Teh Bin Tean
Director, Institute of Biodiversity Medicine
Deputy Medical Director (Research), NCCS

No registration is required.
All are welcomed.