



Indian Institute of Technology Delhi

DEPARTMENT OF BIOCHEMICAL ENGINEERING & BIOTECHNOLOGY

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'Omics' approach reveals lysine succinylation and sirtuin 5 as important regulators of cardiac function

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Protein post-translational modifications (PTMs) add another dimension to the functional diversity of the proteins and allow them to do cellular processes that are otherwise difficult. Despite the variety in structure and cellular localization, PTMs share a common theme: they all use central metabolites as co-substrates. One such PTM is lysine succinylation by succinyl-CoA, which can be reversed by Sirtuin 5 (SIRT5), a NAD⁺-dependent deacylase in mitochondria. Although numerous mammalian proteins undergo this modification, the phenotype of succinylation and SIRT5 remained unknown. In my talk, I will show how a *metabolomics-assisted proteomics* approach guided us to identify the novel phenotype of protein lysine succinylation.

We started out with a targeted metabolomics on acyl-CoAs in various mouse tissues which revealed that succinyl-CoA was the most abundant acyl-CoA in heart. Protein lysine succinylation also increased most dramatically in the heart when *Sirt5* was deleted. That prompted us to perform a quantitative proteomics with heart tissue which identified hundreds of potential desuccinylation substrates of SIRT5. Further biochemical validation showed that trifunctional enzyme subunit alpha (TFE- α), involved in fatty acid oxidation, is a major SIRT5 substrate. *Sirt5* knockout (KO) mice hearts exhibited reduced TFE- α activity, accumulation of long chain acyl-CoAs, and decreased ATP level. Further, echocardiography studies found that *Sirt5* KO mice developed hypertrophic cardiomyopathy. Taken together, these findings identified that a major physiological role of lysine succinylation and SIRT5 is to regulate cardiac metabolism and function. Finally, novel chemical biology approaches including 'omics' tools will be proposed to further advance our understanding on the molecular mechanism of the key regulatory enzymes involved in important PTMs.

All are welcome

Seminar will be held in **DBEB SEMINAR ROOM** at **Block I, Room 223** at **4 PM**
For additional information, contact Seminar coordinator D. Sundar at sundar@dbeb.iitd.ac.in