Possibility of understanding metabolic syndrome by probing dysregulation of metabolic and signaling network in bacteria

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Abstract

High fat diet and high glucose intake are commonly associated with incidence of metabolic syndrome that includes high cholesterol and diabetes. But how the two factors interplay in mediating diabetes remain poorly understood. While animal models could be used to probe the above hypothesized interplay between high fat diet and high glucose intake in mediating diabetes incidence, complex genetic background of the mammalian system seriously hamper the deciphering of the interconnection between phenotype and genes through analysis of functional genomic and epidemiological data. Furthermore, given the high conservation of central carbon metabolism across species between the three domains of life, what are analogs of the effects of high fat and high sugar diets in prokaryotic systems and what metabolic syndromes do they manifest? This work sought to trace the evolutionary ancestry of diabetes and high cholesterol syndrome as manifested in mammalian cells in prokaryotic systems. Using *Escherichia coli* as model organism, this work would heterologously express genes and pathways involved in mammalian fat metabolism in *E. coli* to help understand how a combined high fat and high glucose diet would interact in mediating prokaryotic version of diabetes and high cholesterol syndrome. Insights such as what are the genes differentially expressed during metabolization of high sugar and high fat diet by bacterial cells would hopefully inform the search for mammalian genes that predispose to metabolic syndrome by illuminating hitherto unknown genes and pathways implicated in the disease. But, what is perhaps more interesting from a fundamental perspective in this work is the search for suitable metabolic networks in which to study the prokaryotic version of diabetes and high cholesterol. Could it be overflow metabolism induced by high glucose uptake by *E. coli*? Or could activation of an enhanced lipid recycling pathway serve as a response to high fat infusion in bacteria? More importantly, could the manifested effects of high fat and high sugar diet be vertically inherited in bacteria similar to the incurable high cholesterol and diabetes in mammalian systems? Specifically, does manifestation of diabetes in bacteria results from epigenetic changes that mistune metabolic pathway and networks in an inheritable fashion? Finally, experiments with different types of substrates could be employed to examine the relative impact of high fat diet and high glucose intake on the extent in which central carbon metabolism in *E. coli* would be disturbed. Collectively, heterologous expression of mammalian genes involved in fat metabolism in *E. coli* opens a path to the exploration of prokaryotic version of high cholesterol and diabetes. But, what is perhaps more intriguing is tracing the evolutionary pathway that connects dysregulated sugar and fat metabolism in bacteria to their homologous clinical manifestations in mammalian systems.

Keywords: diabetes, metabolic syndrome, *Escherichia coli*, overflow metabolism, epigenetics, vertical inheritance, mammalian system, transcriptome, fat metabolism, metabolic network,

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