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Epigenetic regulation of insulin gene expression following multigenerational under-nutrition and recuperation

Anand Hardikar
University of Sydney, Australia

Introduction: People in developing countries have faced multigenerational under-nutrition and are currently undergoing major lifestyle changes, contributing to an epidemic of metabolic diseases. The underlying mechanisms remain unclear. We describe how environmental factors (including nutrition and micro-biota) influence metabolic health.

Methods: We use multiple biometric, physiological, metabolic and molecular techniques in two rodent models i) Our recently described Wistar rat model (1) of under-nutrition over 50 generations and nutrient transition and ii) a diet induce adiposity model of high-fat diet. Techniques used include biometry, hyper insulinemic-euglycemic clamps, DEXA, ECGs, cardiac histology, serum biochemistry, immune-histochemistry and multiple molecular techniques including Chromatin Immunoprecipitation (ChIP).

Findings: i) In our multigenerational model, we demonstrate that undernourished rats exhibit low birth-weight, high visceral adiposity (DXA/MRI) and insulin resistance (hyperinsulinemic-euglycemic clamps), compared to age/gender-matched control rats. Undernourished rats also have higher circulating insulin, homocysteine, endotoxin and leptin levels, lower adiponectin, Vitamin B12 and folate levels and an 8-fold increased susceptibility to Streptozotocin-induced diabetes compared to control rats. Importantly, when multi-generationally undernourished rats are provided Control diet, metabolic abnormalities seen in Undernourished rats are not reversed even after two generations of unrestricted access to commercial chow (Recuperation rats). Altered epigenetic signatures in insulin-2 gene promoter region of undernourished rats are not reversed by nutrient recuperation and may contribute to the persistent detrimental metabolic profiles in similar multi-generational undernourished human populations. ii) In diet–induced obesity model, we demonstrate that imbalance in proportions of Bacteroidetes: Firmicutes is associated with metabolic health. We identified that gut levels of short-chain fatty acids are directly proportional to the abundance of butyrate-synthesizing bacteria and offer a metabolic benefit. The levels of short-chain fatty acids in the gut can be manipulated using our novel surgical technique (2) and that this surgery can change gut-bacteria; Firmicutes (33.8% in Obese 4.7% post surgery) and Bacteroidetes (31.4% in Obese 48.1% post surgery). Changes in gut microbiota drive epigenetic modifications at incretin gene promoters, thereby increasing circulating insulin concentrations and changing life-long diabetes risk.

Conclusion: Significance and value of the findings: Our studies demonstrate for the first time as to how i) multigenerational under-nutrition or ii) gut micro-biota influence epigenetic regulation of genes that are critical to metabolic health. Further studies will allow us to understand their importance in similar human cohorts that we plan to assess.

anand.hardikar@ctc.usyd.edu.au