Obesity and gut flora: Link revealed?

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The spreading epidemic of obesity is engulfing not just industrialized nations but developing nations as well. It is also associated with other disorders like type II diabetes, cardiovascular pathology, hypertension and non-alcoholic fatty liver diseases. India is no exception to this and weight gain and obesity are beginning to pose a growing threat to the health of citizens. The reasons attributed to this are industrialization, urbanization, increased living standards, change of diet and life style. But in their recent publication, Backhed et al. make a startling revelation that our gut microbes are responsible for fat deposition in our body.

Influence of gut microbes on human health is not new, it was realized long back. Their sheer number in the gut milieu speaks of their value in human health. In a normal healthy adult, there are as many as 10^{13} microbes in the gut, this is about 10 times the total number of cells present in the human body. There is increasing belief that this microbiota should be viewed equivalent to an ‘organ’, exquisitely tuned to carry out metabolic functions that we are unable to perform ourselves. Like any other branch of microbiology, the components of this microbiota remained poorly defined due to the limitations of being able to culture them in the laboratory. Recently developed approaches based on direct amplification and sequencing of genes like 16S rRNA estimate that total number of different species present in the gut could be 500-1000, this again is equivalent to 100 times more genes than the human genome.

The most prominent member of this community is a Gram-negative anaerobic organism called Bacteroides thetaiotaomi-
RESEARCH NEWS

CTOR. It exists as commensal in the distal intestine of both humans and mice. Earlier analysis of global intestinal transcriptional response has shown that it modulates expression of genes involved in several important intestinal functions including nutrient absorption, mucosal barrier fortification, xenobiotic metabolism, angiogenesis and post-natal intestinal maturation5. Complete genome sequence of this organism is available and the proteome contains 172 glycosylhydrolases that are predicted to cleave most glycosidic linkages encountered in human diets, thus explaining the extraordinary capacity of this organism to acquire and degrade plant polysaccharides6.

Backhed et al.7 take this study further and analyse the role played by these capacities in body fat accumulation. They have done comparative studies on Germ Free (GF) and the mice colonized with conventional microflora (Conventionalized). Interestingly, they found that the mice with microbiota have as much as 42% more total body fat though they consumed 29% less diet. Moreover, if mice that were born Germ Free were introduced, 8–10 weeks after the birth with unfractihoned microbiota obtained from distal intestines of conventionally raised adults, they showed 57% increase in their total body fat.

This was associated with increase in fasting blood sugar levels and insulin-resistant state. Increase in blood sugar levels was understandable with known ability of gut microbes to degrade plant polysaccharides, but how does this result in increased body fat? They further went on to dissect the biochemical pathways and molecular mechanisms behind this intriguing observation. Since glucose and insulin induce synthesis of lipogenic enzymes in liver, they looked at activities of two key enzymes of de novo fatty acid synthesis, acetyl-CoA carboxylase and fatty acid synthetase. Both had increased level in mice containing gut microbes. Likewise levels of transcription factors Steroid Response Element Binding Protein I (SREBP I) and Carbohydrate Response Element Binding Protein (ChREBP) too were higher in these animals. These helix–loop–helix/leucine zipper transcription factors mediate hepatocyte lipogenic responses to glucose and insulin, and are known to act synergistically. Colonized mice had higher level of xylulose-5-phosphate, an upstream regulator of ChREBP. Direct biochemical evidence for increased monosaccharide uptake by ‘Conventionalized’ mice was obtained by measuring 2-deoxy-glucose levels. These mice not only have an increased uptake but also higher density of blood capillaries in the intestine, thus further facilitating the transfer of absorbed monosaccharide to portal circulation.

Thus it is clear that gut microbes metabolize plant polysaccharides and induce lipogenic activity in liver. The numbers of fat cells in the fat pads of Germ Free and Conventionalized mice were same, as evidenced by DNA content, which means that increased fat content is due to growth in the size of these cells rather than number. Lipoprotein lipase (LPL) is key regulator of fatty acid release from triglycerides in liver and other organs. Its activity was 122% more in epididymal fat pads and 99% higher in heart of Conventionalized mice. It is regulated by Fasting-induced adipocyte factor (Fiaf), a member of the angioptatin-like family of proteins and is an inhibitor of LPL. It is induced in GF animals during suckling–weaning transition and this transition does not occur in Conventionalized mice, leading to continued expression of LPL. During suckling–weaning transition, the diet changes from lactose–lipid rich milk to low fat polysaccharide rich chow. This period is also concomitant with expansion of the microbiota and shift from facultative to anaerobic flora. The authors conclude that gut microbiota regulate LPL activity by mediating expression of Fiaf, this was further confirmed in mice where Fiaf is inactivated by gene disruption (knock out). The Conventionalized knock out mice have the same body fat as their GF controls. This establishes role of Fiaf as key mediator of body fat regulation by microbiota. The microbiota stimulate hepatic triglyceride production through transcription factors such as ChREBP and promote incorporation of these in adipocytes through transcriptional suppression of LPL inhibitor, i.e. Fiaf.

These studies indicate that human and gut microbes have co-evolved a symbiotic relation and one manifestation of this is ability of microbes to process dietary components and deposit extracted energy in the form of fat. This ability of storage could be of paramount importance to ancient humans who had variable access to food. Microbiota enabled them to draw maximum energy from available diet, store extra energy in the form of fat which could be utilized when in need. But in the modern day life, where food is not scarce, this benefit becomes detrimental. The authors further speculate that changes in microbial ecology promoted by western diets and difference in the microbial ecology of individuals in these societies could be the ‘environmental factors’ that affect predisposition towards obesity.


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544 CURRENT SCIENCE, VOL. 88, NO. 4, 25 FEBRUARY 2005