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Editorial Article

Paradigm Shift of Obesity Research

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Obesity is the state that excessive fat is accumulated to the adipose tissue. Simple clinical marker of obesity is body mass index that is higher than 25~30 kg/m^2. Medical intervention is necessary when the obesity is characterized by an excessive visceral fat accumulation or has comorbidities including such as diabetes, hypertension, dyslipidemia, coronary artery disease. Over-nutrition and lack of exercise are the most common cause of obesity. Mutations of genes including melanocortin receptor 4 or leptin receptor have been reported as monogenic causes of obesity, but it is quite small in population. Genome wide association study uncovered several obesity related gene SNPs, e.g., FTO. However, the ratio that can explain obesity by a genetic background is up to 10%.

On the other hand, the non-communicable diseases including obesity are more prevalent after growing the children born under starvation of the wartime in Netherlands. The epidemiological investigations by Barker D et al. [1] confirmed these evidences as developmental origins of health and disease (DOHaD). Subsequently, the mechanism is being clarified. One of the acceptable mechanism is that epigenetic programing by hypo-nutrition is disrupted by over-nutrition after birth, leading to the dysregulation of energy metabolism.

More than 10^{14} bacteria existed in the human gut. Species of enteral flora and association with the obesity came to attract attention in 2006 because technology of metagenome analysis has dramatically developed and more easily identified and classified species of gut microbiota. It was reported that the microbiota ratio of the Bacteroidetes group decreased and that the ratio of the Firmicutes group increased in the feces of subjects with obesity [2]. However, there are many confounding factors in human, so it is still controversial which intestinal microbiota is related to obesity [3]. When the intestinal microbiota of the obesity mouse were transferred into a non-obese mouse, the non-obese mouse became obese [4]. When the intestinal microbiota in a lean person was transferred to a person with metabolic syndrome, insulin sensitivity improved in the subject with metabolic syndrome [5]. These evidences indicate that the relation between gut microbiota and obesity is not a simple relation but a causal relation.

Influence of gut microbiota on energy metabolism is becoming clear (Fig.1). The intestinal microbiota ferments cellulose and produces short-chain fatty-acids (SCFA) including acetic acid, butyric acid, and propionic acid. These SCFA acts as a ligand on G protein-coupled receptor (GPR) 41 of the intestinal epithelial cells, and stimulates peptide YY production, thereby inhibiting intestinal motility and promoting the energy collection from gastrointestinal tract [6]. On the other hand, the absorbed SCFA acts on GPR43 of the white adipocytes to inhibit an insulin signal and to restrain fat accumulation [7]. Therefore, the disturbed gut microbiota (dysbiosis) causes a reduction of SCFA production and fat accumulation. Angiopoietin-like protein 4 (Angptl4) is expressed in the intestinal epithelium and is released into the circulation. Thereafter, angptl4 inhibits the lipoprotein lipase (LPL) activity of the fat cell. The unfavorable intestinal microbiota inhibits expression of Angptl4 in gut epithelium and promotes fat uptake in the white adipocytes by raising their LPL activity. In addition, this action was different in degree by gut microbiota species [8].

The action of gut microbiota on chronic inflammation is also being clarified (Fig.1). It is known that SCFA produced by gut

microbiota binds to GPR43 of the gut epithelial cells and induces the antiinflammatory action on immune cells such as macrophage. Therefore, the reduction of SCFA by the change of gut microbiota causes chronic inflammation. In addition, high-fat meals changes the gut microbiota which produces endotoxin, lipopolysaccharide (LPS). LPS binds to CD14 of macrophage and causes chronic inflammation and insulin resistance [9].

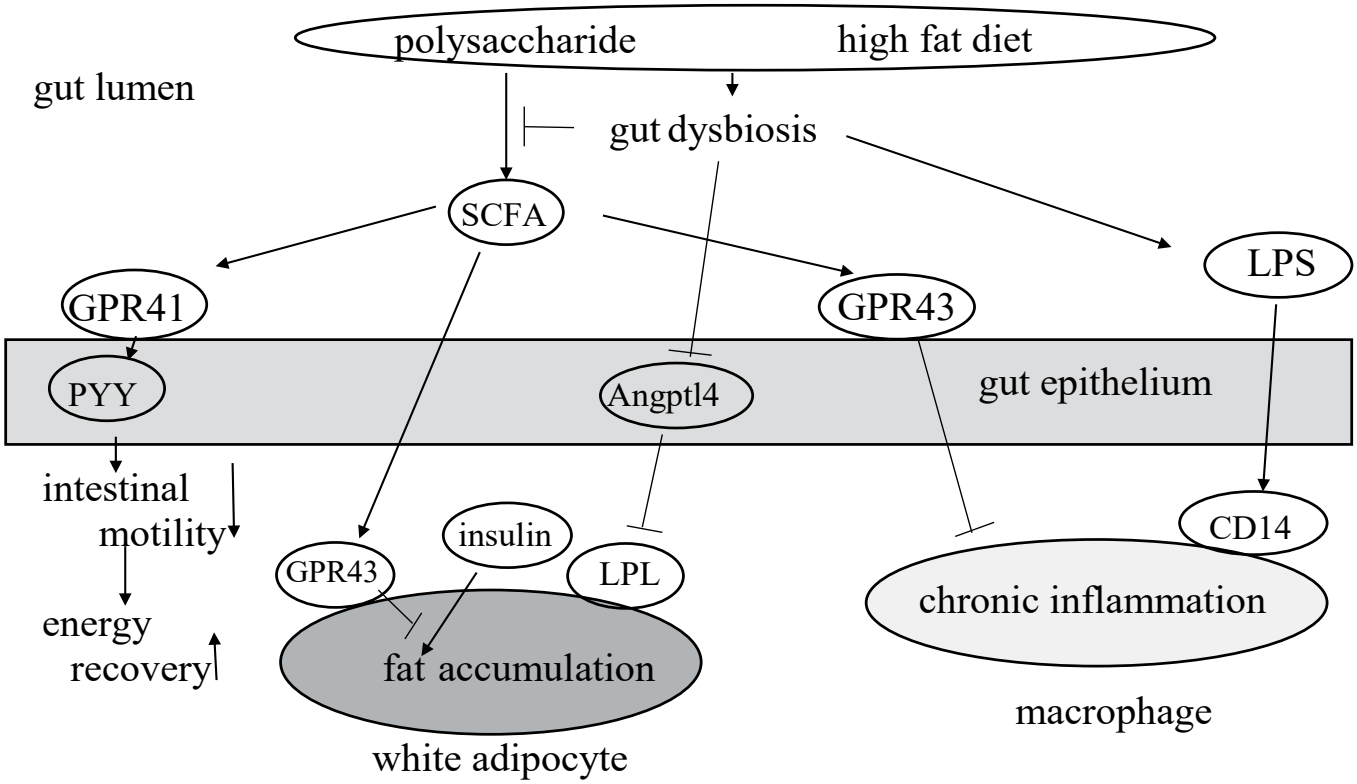

Figure 1. Mechanism of fat accumulation and chronic inflammation induced by gut dysbiosis
SCFA; short chain fatty acid, GPR; G protein-coupled receptor, PYY; peptide YY, Angptl4; angiopoietin-like protein 4, LPL; lipoprotein lipase, LPS; lipopolysaccharide

The obese control is not easy, but the improvement of dysbiosis might be a promising strategy against obesity. Transfer of intestinal microbiota [5] or bariatric surgery [10] are effective to improve gut dysbiosis. It is to be elucidated in a future what kind of prebiotics (nutrition), probiotics, and biogenics are potentially effective to improve gut dysbiosis for protection against obesity.

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