Role of DNA methylation in early life and its impact in later life

Nutritional environment in the fetal and neonatal periods might affect the susceptibility to adult-onset metabolic diseases such as obesity and type 2 diabetes, which may be referred to as the “Developmental Origins of Health and Disease (DOHaD)” hypothesis. However, its detailed molecular mechanism has been ill-defined.

The liver is a major organ of lipid metabolism, which is markedly changed in response to physiological nutritional demand. We provided evidence that ligand-activated PPARα-dependent DNA demethylation regulates the fatty acid β-oxidation genes in the postnatal liver (Diabetes 64: 775-784, 2015). Given that PPARα is known to be activated in the liver in response to milk-derived lipid ligands during the suckling period, it is likely that milk lipids serve as a nutrient signal during the neonatal period, so that they can be oxidized efficiently as an energy source.

Fibroblast growth factor 21 (FGF21; Fgf21) is a major PPARα target gene that occurs in the liver. We have found that DNA demethylation of Fgf21 can be modulated and/or enhanced by pharmacologic activation of PPARα during the suckling period. Importantly, DNA methylation status of Fgf21, once established in early life, is relatively stable and remains into adulthood as an epigenetic memory. With increased DNA demethylation, hepatic induction of Fgf21 has been exaggerated upon PPARα activation, which may account in part for the attenuation of diet-induced obesity in adulthood. This study represents the first demonstration that DNA methylation status of a particular gene, once established in early life, contributes to the phenotypes in later life.

Selected Publications

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  <Wako: 408 Seminar Room, Chemical Biology Bldg.>
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