Intrauterine Poor Nutrition and Adult Diseases

In the past two decades evidence has accumulated from epidemiological, clinical, and animal studies which supports the association between intrauterine poor nutrition and the risk of developing obesity, type 2 diabetes, cardiovascular disease, and other chronic diseases in later life. These findings have been confirmed in multiple populations and in numerous animal studies in multiple species. It is clear that the environment of mother, baby, and child is a key contributor to diseases and conditions that account for approximately one third of the global burden of disease in both developed and developing countries. Such a relationship between insults during development and later onset of disease has been proposed as “developmental origins of health and disease (DOHaD).” During these two decades the rate of low birth weight (<2,500 g) newborns in Japan has doubled from 5% to 9.6%, producing approximately 100,000 infants with potential risk of later onset of adult diseases every year. Although adverse antenatal and postnatal environments increase the risk of particular adult diseases, the occurrence of the eventual outcome depends largely on individual genotype. Therefore, it has been suggested that gene-environment interactions underlie the DOHaD.

Predictive Adaptive Responses and Epigenetic Regulation of Transcription

Many diseases have their origin in utero. The irreversible plastic changes made as a result of gene-environmental interactions during the fetal period may turn out to be altogether inappropriate later in life. This occurs when the egg/embryo/fetus perceives its future environment to be within a certain range only to find out it has been born into an entirely different environmental range. For example, when a fetus is exposed to nutritional deficit in utero, it will make phenotypic adaptive responses in anticipation of a future poor nutritional environment, modifying its metabolism to become a thrifty phenotype, only to discover it has been born into an environment of nutritional excess. Such a predictive adaptation in utero which is mismatched with its later improved environment is thought to put the fetus at risk of developing obesity, type 2 diabetes, and other adult diseases in later life when it is exposed to high fat diet and insufficient physical exercise in modern lifestyle. Such a fetal response is named ‘predictive adaptive responses.’

Predictive adaptive responses are phenotypic modulations with altered gene transcription. Gene transcription during fetal period is affected by various stimuli including maternal nutrition, hypoxia, oxygen stress, etc. Such a modulation of gene transcription is mediated through alteration of expression of transcription factors which regulate multiple steps of organogenesis and establishing metabolic functions. These changes in multiple gene expressions ultimately result in phenotypic alteration and disease susceptibility.

The mechanism by which transcription is regulated without alteration of DNA sequence during development in utero is postulated to be through epigenetic regulation, which determines the timing and intensity of expression of specific genes by modulating chromatin conformation. The chromatin conformation can be modified mainly through methylation or demethylation of the cytosine base in CpG island of DNA, and acetylation or deacetylation of the amino termini of histones.

Intergenerational Transmission of Altered Epigenetic Gene Regulation

Numerous animal studies show that F₀ environment-
tal perturbations during pregnancy can have phenotypic effects that mimic adverse human health consequences not only on the F₁ offspring but also on the F₂ offspring as well. Perturbations include dietary manipulations, enforced physical activity, exposure to hormones or endocrine disruptors, etc. Adverse health outcomes include obesity, hypertension, insulin resistance, development of tumors, etc. These perturbations often cause epigenetic changes in DNA methylation or histone acetylation, which provide the potential mechanism of observed phenotypic changes. Dietary challenges in F₀, such as low protein diet, produce such epigenetic alterations in gene expression that can affect energy metabolism in F₂ without further challenge in F₁ females.

Some of these effects are transmitted to multiple subsequent generations through the germ line. The best current explanation for these findings is that they are initiated by F₁ epigenetic processes which are resistant to elimination after F₂ conception. Adequate data on human population to address intergenerational transmission are scarce because of the long-term follow-up and the limitation of observational studies in humans. It is necessary to accumulate clinical data to elucidate mechanisms of intergenerational transmission of altered phenotype in humans, because a vicious cycle of intergenerational amplification of obesity, diabetes, and cardiovascular disease may further proceed in the next several decades.