Epigenetics: Reprogrammable interface of the genome and environments

In the past decade, the genes involved in the pathogenesis of type 1 and type 2 diabetes have been identified by a comprehensive search over the whole genome, the genome-wide association study (GWAS). The method is now carried out by a dramatically improved technique to detect single nucleotide polymorphisms (SNPs) with different frequency between the control and the disease group. SNP, however, is not an universal disease-marker that can be used in any case. For different ethnicities in particular, it is necessary to clarify the difference of the contribution of the gene. Therefore, data of Asian populations would be as significant, and this Journal is considered to further increase the importance in this field. In clinical applications of gene-based medicine, it is also necessary to carry out a longitudinal study of these candidate genes. Even with the genome-wide study, we cannot apply the information to an individual patient. Genetic taylor-made medicine will become possible only when evidence is obtained by carrying out a longitudinal prospective study on the gene of interest.

Recently, a new additional area called ‘epigenetics’ has emerged in the field of complex genetic diseases, including diabetes mellitus. Epigenesis refers to a process that is based on the information marked on the genome after fertilization, primarily in animals. This has been elucidated as a mechanism of cellular function, specifically the pattern of gene expression through change of chromatin structure instead of change in the nucleotide sequences. Biochemical entities of the epigenetic marks include deoxyribonucleic acid (DNA) modifications, such as 5-methylcytosine at CpG sites, and post-translational modifications of histones methylation, acetylation and phosphorylation. These are subject to being erased throughout the entire genome in germ line cells, but it comes to appear again after fertilization, and will change according to the specific cellular environment and differentiation. With the exception of this process, epigenetic status can be determined according to parental origin of the allele for genomic imprinting, and can be determined randomly for X chromosome inactivation. Importantly, epigenetic system ensures two outstanding property at the same time. First, the systems shows robust epigenetic memory that is crucial for maintenance of cellular differentiation states even through the process of somatic cell division. Second, the system applies the flexibility of chromatin states to adaptation and responses to various environmental challenges from outside the cell.

**Figure 1** | Schematic presentation of epigenetic and environmental process of β-cell senescence. Three major factors of cellular senescence (INK4a-ARF, deoxyribonucleic acid [DNA] damage and telomere loss) are known as Hayflick factors. Of these, the cell-cycle regulator, p16INK4a, is an inhibitor of the cyclin-dependent kinases CDK4 and CDK6, and acts by arresting a G1-S transition. The other de-repressed factor, p19ARF, regulates p53 stability through inactivation of the p53-degrading ubiquitin ligase, MDM2.
So, what gene region should we observe to find alterations in an epigenome for etiology and new regenerative medicine? A simple method is to analyze known candidate genes. Most of the associated genes of type 2 diabetes found by GWAS appear to have the potential to regulate β-cell mass and function. In fact, studies on candidate genes including peroxisome proliferator-activated receptor gamma gene, the insulin gene promoter and the pancreatic and duodenal homeobox 1 gene promoter identified epigenetic alterations in pancreatic islets of patients with type 2 diabetes. Alternatively, comprehensive studies that address the role of epigenetic alterations in the pathogenesis of type 2 diabetes in humans have recently commenced to uncover genes with differential DNA methylation in diabetic islets compared with controls. The approach for screening the open chromatin with gene activity or non-coding ribonucleic acid (RNA) has been used for genome-wide epigenetic analysis. These techniques have allowed researchers to map epigenetic marks with gene activity, or the transcribed long non-coding RNAs. The results show a new class of islet genes providing a new impact on the pathophysiology of diabetes.

As observed in many Asian countries, the prevalence of type 2 diabetes in the population where the incidence of type 2 diabetes was once low is now increasing greatly in accordance with the change of nutritional status. The genes responsible for metabolic control might alter their expression patterns through alterations of epigenetic status and adapt to the nutritional change, but the precise mechanism of this epigenetic reprogramming is not fully clarified. Strong epidemiological and experimental evidence shows a link between intrauterine growth restriction and adult diseases, such as type 2 diabetes. This is thought to be an example of the changes in epigenetic programming as a result of nutritional status.

Another important concept of epigenetic phenomena in diabetes is the age-associated alteration of epigenetic status, specifically of genes in pancreatic β-cells. Islet β-cells can expand during embryonic development and the neonatal period in humans and experimental animals, but the ability of proliferation subsequently decreases. The disability of β-cells to divide for renewal in later life is thought to be based on cellular senescence, which mainly contributes to the aging phenotype in general. Three molecular mechanisms of cellular senescence that have attracted attention include: (i) upregulation of the cyclin-dependent kinase inhibitor, p16INK4a; (ii) accumulation of oxidative DNA damage; and (iii) telomere shortening (Figure 1).

Prior studies suggest that the Polycomb group (PcG) protein enhancer of zeste homolog 2 (Ezh2) functions as a histone methyl-transferase (H3K27 trimethylation; H3K27me3), and is an epigenetic regulator of critical genes, embryonic development, stem cell renewal and cellular senescence. Most importantly, Ezh2 represses the INK4a/ARF locus as a target gene region in islet β-cells through epigenetic alterations in a time-dependent manner. Thus, the epigenetic investigation of the failure in β-cell regeneration through the INK4a/ARF locus and PcG protein might elucidate underlying diabetes pathogenesis.

Finally, epigenetic studies can provide novel regenerative medicine. Now researchers are beginning to think that they could investigate the ability of β-cell self-renewal independently of its differentiation status by attributing an epigenetic status that is reprogrammable. Furthermore, a recent study suggested that the epigenetic memory might predispose even β-cell derived-induced pluripotent stem cells to differentiate more readily into insulin-producing cells. If epigenomic manipulation becomes possible, the reprogramming of patients’ cells should provide novel regeneration therapies for diabetes.

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