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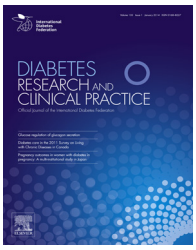

Review

Role of epigenetic mechanisms in the development of chronic complications of diabetes

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ABSTRACT

There is growing evidence that epigenetic regulation of gene expression including post-translational histone modifications (PTHMs), DNA methylation and microRNA (miRNA)-regulation of mRNA translation could play a crucial role in the development of chronic, diabetic complications. Hyperglycemia can induce an abnormal action of PTHMs and DNA methyltransferases as well as alter the levels of numerous miRNAs in endothelial cells, vascular smooth muscle cells, cardiomyocytes, retina, and renal cells. These epigenetic abnormalities result in changes in the expression of numerous genes contributing to effects such as development of chronic inflammation, impaired clearance of reactive oxygen species (ROS), endothelial cell dysfunction and/or the accumulation of extracellular matrix in the kidney, which causing the development of retinopathy, nephropathy or cardiomyopathy. Some epigenetic modifications, for example PTHMs and DNA methylation, become irreversible over time. Therefore, these processes have gained much attention in explaining the long-lasting detrimental consequences of hyperglycaemia causing the development of chronic complications even after improved glycaemic control is achieved. Our review suggests that the treatment of chronic complications should focus on erasing metabolic memory by targeting chromatin modification enzymes and by restoring miRNA levels.

Contents

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1. Introduction

Economic growth accompanied by changes in the dietary and physical behavior of individuals can dramatically increase the risk of developing metabolic disorders, including diabetes mellitus (DM) with its associated chronic complications. An individual's hyperglycemic status is associated with oxidative stress, activation of the polyol pathway, increased flux in the hexosamine pathway, the accumulation of advanced glycation end-products and lipid abnormalities [1,2] can lead to the development of diabetes-specific microvascular complications such as diabetic nephropathy (DN), neuropathy, and diabetic retinopathy (DR), and macrovascular complications such as atherosclerosis and diabetic cardiomyopathy [3,4].

Genetics factors are believed to be essential for the development of various types of DM and its associated chronic complications [5,6]. However, these genetic factors alone cannot explain the development of DM and its complications [7], which suggests the involvement of abnormal epigenetic mechanisms in these processes [8–10]. Moreover, it has been demonstrated that complex interactions between various genes and the environment are implicated in some changes in gene expression and in the occurrence of chronic complications [11,12]. Therefore, the epigenetic mechanisms involved in the regulation of gene expression including post-translational histone modifications (PTHMs), DNA methylation and microRNA (miRNA)-regulation of mRNA translation appear to play a crucial role in the development of DM associated complications [13–15].

2. Epigenetic modifications

The term 'epigenetic' was originally defined by C. H. Waddington in 1938 as ''the causal interactions between genes and their products, which bring the phenotype into being'' [16]. Currently, the term 'epigenetic' refers to the study of heritable traits of gene expression and subsequent phenotypic changes that do not include alterations of DNA sequences [17]. Therefore, the study of epigenetics focuses on the mechanisms by which the environment interacts with the genotype to produce a variety of phenotypes by either modification of chromatin structure or control of mRNA translation [18,19].

Chromatin is a complex of DNA and proteins, primarily histones, and is considered to be the major site affected by epigenetic factors. The dynamic arrangement between the transcriptional 'active' (euchromatin) and 'inactive' (heterochromatin) status of chromatin in response to extracellular

Table 1 – Enzymes involved in post-translational histone modifications (PTHMs) and chromatin remodeling.

Groups of PTHMs enzymes	Subgroups of PTHMs enzymes	Type of PTHMs	Residues Modified	Chromatin structure	Ref.
HATs	ATF-2 GCN2,5 HAT1 TIP60 Rtt109	Acetylation	H4K8, H4K16 H2BK11, H2BK16, H3K9, H3K14 H2AK4, H2AK7, H4K12 H2AK5, H3K14, H4K12 H3K56	Ech	[33] [34]
HDACs	HDAC1-11 SIRT1-7	Deacetylation	H2AK2, H3K56, H4K16, H4K5	Hch	[29] [30] [34]
HMTs	CARM1 PRMT1 SUV38h1, SUV39h1 SET7/9, SUV420h2,	Methylation	H3R17 H4R3 H3K9 H4K20	Ech	[30] [33] [34]
KDM	LSD1	Demethylation	H3K4, H3K9	Ech	[30]
Ubiquitilases	RNF20/40	Ubiquitination	H2BK120	Ech	[34]

ATF-2 – activating transcription factor 2, CARM1 – histone arginine methyltransferase, Ech – euchromatin, GCN2\5 – general control no repressed kinase 2\5, H – histone, HATs – histone acetylotransferases, Hch – heterochromatin, HDACs – histone deacetylases, HMTs – histone methyltransferase, K – lysine, KDM – histone lysine demethylases, LSD1 – lysine specific demethylase 1, PRMT1 – protein arginine methyltransferase 1, R – arginine, RNF20/40 – ring finger protein 20/40, Rtt109 – Ty1 transposition gene product 109, SET7/9 – SET domain-containing protein 7, SIRT–sirtuins, SUV38h1 – suppressor of variegation 3–8 homolog 1, SUV39h1–suppressor of variegation 3–9 homolog 1, SUV420h2 – suppressor of variegation 4–20 homolog 2, TIP-60 – Tat-interactive protein 60 kDa.