HDAC Allostery: A Therapeutic Target for the Management of Diabetes and Its Complications

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Abstract

$ IHZ GHFDGHV DJR 'LDEHWHV 0HOOLWXV '0   DV ZHOO DV LWV FRPSOLFDWLRQV
PHGLFDO DQG HFRQRPLF VHFWRUV RI

the autoimmune breakdown of the B-cell present at the islet of Langerhans in the pancreas [11]. This destructive process is initiated by the T-cells of the immune system. As a result, the strong odor of acetone is one of the symptoms of diabetes in children, which is known as ketoacidosis. Athar et al. reveal that factors such as genetics, auto-immune dysregulation, and lifestyle (nutrition) are predisposing parameters in the etiology of T1DM [12], but it should be noted that viral infection also plays a critical role [13]. Coxsackie B4 virus, an RNA virus, has been implicated in the destruction of the B-cells of the islet of Langerhans. The molecular mechanism of this process can be illustrated as follows: an enzyme located on the surface of the islet of Langerhans, called Glutamic Acid Decarboxylase (GAD), has a similarity to the protein present in coxsackie virus B4, called Protein 2C (P2C). Due to this similarity, p2C is seen as self and left un-attacked by the T-cells, thus enhancing the destruction of B-cells. This isn't usually the case in T2 DM [14].

Type 2 diabetes mellitus: This form of DM is more prevalent than type 1 DM. This form of DM is characterized by an elevated level of both insulin and glucose in the blood [15]. Unlike in T1DM, where there is a breakdown of B-cells, the physiology of B-cells in T2DM is usually kept intact. Like T1DM, the etiology of T2DM can be traced to genetic, lifestyle, and environmental factors [16]. In T2DM, there is insulin secretion, but the Glucose Transporters (GLUT) at the membrane surface of most cells are resistant or non-responsive to this secreted insulin, leading to insulin resistance. This is exacerbated due to no further production of insulin to compensate for the resistivity of the insulin earlier produced [17]. There is elevated blood glucose in patient affected by T2DM for a period of time but shows no symptoms of diabetes, in this individual, there is usually no need of insulin injection for survival. T2DM has a prevalence of about 90–95% of DM cases globally. A correlation exists between T2DM and obesity,] expression and maintain the homeostasis of the cell. Acetylation, methylation, and phosphorylation are the modification factors that regulate the process of transcription, but the most understood among these processes is the acetylation process [24]. Deacetylation or methylation increases the net positive charge of histone which represses the binding of transcriptional factors, and thus downregulating the process of gene expression. On the hand, acetylation increases the net negative charge of histone proteins, thereby reducing the affinity of DNA for histone and this gives chance for the accessibility of RNA polymerase ll.

A stretch of about 390 amino acids makes up the catalytic domain of HDAC. The active site of HDAC, is made up of evolutionarily conserved amino acids and consists of a slightly curved pocket-like strucvM or § f m0hanľ/ M bE