TARGETING DNA METHYL TRANSFERASE 1[Dnmt1]- IN DIABETIC NEPHROPATHY

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ABSTRACT
Dnmt1 is necessary for HDACs activity and recruits various HDACs and transcription factor responsible for podocyte injury in Diabetic nephropathy, targeting Dnmt1 may prevent podocyte injury and decrease albuminuria, mesangial matrix expansion and glomerular hypertrophy. Hence Dnmt1 are novel targets.

KEYWORDS: Dnmt1, DN-DIABETIC NEPHROPATHY, HDACs, HDACI.

INTRODUCTION
In mammals, DNA methyltransferase 1 (Dnmt1)\(^9\) is responsible for replicating the pattern of CpG methylation from the parental DNA strand to the daughter strand during DNA synthesis,\(^{1,2}\) thereby maintaining DNA methylation during cell replication.

DNA methylation mediates its effects directly by blocking access of key transcription factors to their DNA binding positions, or indirectly through epigenetic control of their access to DNA through alterations in chromatin structure.\(^{3,4}\)

The current model linking DNA methylation to chromatin remodelling occurs through recognition of methyl-CpG by DNA methyl-binding proteins (i.e., MeCP2 and MBD2) that in turn activate histone deacetylase (HDACs)activity and linked nucleosome remodelling proteins to form chromatin remodelling complexes.\(^{5,6,7,8}\) These complexes directly affect the degree of DNA coiling, and act to strengthen the pattern of gene expression set by DNA methylation through formation of transcriptionally silent heterochromatin.
PATHWAY
Sp1/NFκB-p65 complex in Dnmt1 regulation was confirmed by the observation that Sp1 knockdown using mithramycin A or siRNA decreased Dnmt1 protein levels. The luciferase assay additionally indicated that Dnmt1 was a direct target of Sp1.[16]

ROLE
DNA METHYLATION –RECRUIT HDACS ACTIVITY

HYPERGLCEMIA ACTIVATES HDAC

RETINOPATHY ROLE:- Hyperglycemia stimulated HDAC and augmented HDAC1, 2, and 8 gene expressions in the retina and its capillary cells. The activity HAT was negotiated and the acetylation of histone H3 was reduced. Cessation of hyperglycaemia failed to provide any benefits to diabetes-induced changes in retinal HDAC and HAT and histone H3 remained subnormal. This put forward “in principle” the role of global acetylation of retinal histone H3 in the progress of diabetic retinopathy and in the metabolic memory phenomenon accompanying with continued progression.[10]

KIDNEY/RENAL DISEASE AND FIBROSIS[11,12]

HAT activity is also associated with the development and progression of some chronic diseases characterized by fibrosis, including chronic kidney disease, cardiac hypertrophy, and idiopathic pulmonary fibrosis.[11]

HDAC 2 PLAYS IMPORTANT ROLE IN DN[13]

Among the six HDACs verified (HDAC-1 through -5 and HDAC-8), HDAC-2 activity amplified in the kidneys of STZ-induced diabetic rats and db/db mice and TGF-β1-treated NRK52-E cells.[13]

Remarkably, hydrogen peroxide amplified HDAC-2 activity, and the management with an antioxidant, N-acetylcysteine, almost totally reduced TGF-β1-induced activation of HDAC-2. These findings advocate that HDAC-2 plays an key role in the progress of ECM accumulation and EMT in diabetic kidney and that ROS mediate TGF-β1-induced activation of HDAC-2.[13]

HDAC 4 PLAYS IMPORTANT ROLE IN DN[14]

Zinc-dependent HDACs, HDAC2/4/5 were up-regulated in the renal tissue from streptozotocin-induced diabetic rats, diabetic db/db mice, and in renal biopsies from diabetic
patients. Podocytes on treatment with high glucose, advanced glycation end products, or transforming growth factor-β (common injurious factors in diabetic nephropathy) selectively augmented HDAC4 expression. The role of HDAC4 is assessed by in vivo gene silencing by intrarenal lentiviral gene delivery and found to decrease renal injury in diabetic rats. Consequently, HDAC4 adds to podocyte injury with overwhelming autophagy and exacerbating inflammation by HDAC4-STAT1 signalling in vitro and is one of critical components of a signal transduction pathway that links kidney injury to autophagy in diabetic nephropathy.[14]

**HDAC9**[15]

HDAC9 and found that HDAC9 expression was significantly up-regulated in high glucose (HG)-treated mouse podocytes, as well as renal tissues from diabetic db/db mice and patients with DN.[15]

In diabetic db/db mice, silencing of HDAC9 diminished the glomerulosclerosis, inflammatory cytokine release, podocyte apoptosis and kidney injury. Collectively, these data indicate that HDAC9 may be tangled in the process of DN, especially podocyte injury. The study propose that inhibition of HDAC9 may have a therapeutic potential in DN treatment.[15]

**ANIMAL STUDY**[16]

In vivo and in vitro under the diabetic state, the expression of DNA methyltransferase 1 (Dnmt1), nuclear factor Sp1, and nuclear factor kappa B (NFκB)-p65 evidently augmented in podocytes. The amplified expression of Dnmt1 was decreased after treatment with 5-azacytidine or 5-aza-2′-deoxycytidine or knockdown of Dnmt1 restored decreased podocyte slit diaphragm proteins following from hypermethylation and enhanced podocyte motility. Additional studies found that augmented Sp1 and NFκB-p65 interacted in the nucleus of podocytes incubated with high glucose, and Sp1 bound to the Dnmt1 promoter region.[16]

**EFFECT OF Dnmt1 inhibitors**[16]

Albuminuria in a db/db mouse model was evidently decreased after treatment with a DNA methylation inhibitor. This was attended by mitigation of glomerular hypertrophy, mesangial matrix expansion, and podocyte injury.[16]
**BENEFITS/ADVANTAGES OF DNMT1 INHIBITOR**

1. Prevents the activation of various HDACs enzymes contributing to diabetic nephropathy.
2. Decreases albuminuria.
3. Prevents fibrosis.
4. Prevents podocyte injury and apoptosis.
5. Decrease mesangial matrix expansion.
6. Prevents glomerular hypertrophy.
7. May be helpful in retinopathy.
8. Since many isoforms of HDACs are up-regulated in diabetic nephropathy it’s very difficult to target specific HDACs in such condition targeting Dnmt1 inhibitor are handy tool.
9. SP1 and NF-κB interaction in response to high glucose may be inhibited by Dnmt1 inhibitors.
10. Dnmt1 Inhibitors restores erythropoietin production in fibrotic murine kidney\(^{17}\), thus in can be used to treat CKD and also prevent anaemia in such patient further studies are necessary.

Dnmt1 inhibitor are quite superior to HDAC inhibitors.

Thus Dnmt 1 is potential drug target for diabetic nephropathy and further study are needed.

**CONFLICT OF INTEREST**
The Author Declares there is no conflict of interest regarding publication of this paper.

**DECLARATION**
The author has not conducted any animal study or Human Trial, the matter in the article is which comprises animal or human trial are the study done by researcher /scientist listed in the Reference section and cited appropriately and are taken up in the article to support the Hypothesis.

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I give credit to all authors listed in my reference list and acknowledge them for Nobel work.
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