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Review Article

CRISPR-dCas9-mediated CpG island editing: A potential game-changer for diabetes treatment

Khokon Kumar Dutta[1]

[1] *Department of Biochemistry and Molecular Biology, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj-8100, Dhaka, Bangladesh*

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia. Current therapeutic strategies primarily manage symptoms, leaving a substantial unmet need for curative interventions. This review explores the potential of CRISPR-dCas9-mediated CpG island editing as a promising therapeutic approach for T2DM. CpG islands, DNA regions enriched in cytosine-guanine dinucleotides, play a pivotal role in gene regulation. Their methylation status significantly influences gene expression. By targeting specific CpG islands within genes involved in glucose metabolism and insulin signaling, CRISPR-dCas9 can modulate gene expression and restore metabolic homeostasis. A particular focus is placed on the TXNIP gene, implicated in T2D pathogenesis. Reprogramming TXNIP expression using CRISPR-dCas9 offers potential therapeutic benefits, including protecting pancreatic beta cells, enhancing insulin sensitivity, and mitigating inflammation. While the potential of CRISPR-dCas9-mediated CpG island editing is clear and evident now, further steps are imperative to translate this approach into effective and safe therapies for T2DM patients.

1. Introduction

Advances in epigenetic editing technology have paved the way for novel therapeutic approaches in various diseases, including diabetes. One promising approach is the CRISPR-dCas9-mediated editing of CpG islands, which could potentially target gene expression through epigenetic modifications. This review explores the role of CpG islands, their involvement in gene regulation, and how CRISPR-dCas9 can be used to edit these regions for potential diabetes treatment, focusing specifically on the TXNIP gene.

CpG islands are short stretches of DNA that are densely packed with cytosine-guanine (CpG) dinucleotides. They are commonly found near gene promoters, playing a critical role in gene regulation due to their influence on transcriptional activity (Bird *et al.*, 1985; Bird, 1986). The unique feature of CpG islands is their high CpG density, their largely unmethylated state, and their strong association with active gene promoters (Gardiner-Garden and Frommer, 1987). Methylation of CpG islands, however, can lead to transcriptional silencing, making these regions key targets in epigenetic regulation.

Several computational tools have been developed to identify CpG islands within genomic sequences, including CpG Island Searcher, IslandPicker, and PromoterScan (Deaton and Bird, 2011). These tools use algorithms that search for high CpG density, appropriate sequence length, high GC content, and an observed/expected CpG ratio greater than a specific threshold (Choy *et al.*, 2010). These features are essential for accurate identification and analysis of CpG islands, particularly in their role in regulating gene expression.

DNA methylation, the addition of methyl groups to the cytosine base in CpG dinucleotides, is a powerful epigenetic modification that silences gene expression when it occurs in gene promoters (Lee and Lee, 2012). Methylation interferes with transcription factor binding and recruits proteins that compact chromatin, thus reducing gene expression. Conversely, unmethylated CpG islands are typically associated with actively transcribed genes (Lee *et al.*, 2015; Yoo *et al.*, 2021). Factors influencing CpG island methylation include DNA methyltransferases (DNMTs), Ten-Eleven Translocation (TET) enzymes, chromatin accessibility, and environmental conditions.

In Dutta *et al.* (2005), identified a CpG island within the TXNIP gene's promoter region. This CpG Island, rich in cytosine and guanine dinucleotides, is a common target for epigenetic modifications, particularly DNA methylation. DNA methylation, the addition of a methyl group to cytosine residues in CpG dinucleotides, typically silences gene expression by hindering transcription factor binding or promoting chromatin compaction. Aberrant methylation patterns are implicated in various diseases, including diabetes.

Dutta *et al.* (2005) pioneered the discovery that hypermethylation of this CpG island correlates with decreased TXNIP expression in kidney cancers. Conversely, under normal conditions, the CpG Island is typically hypomethylated, leading to increased TXNIP levels. This dynamic regulation is essential for maintaining balanced cellular proliferation in both normal and cancerous kidney tissues (Dutta *et al.*, 2005; Kim *et al.*, 2021; Zhang *et al.*, 2017).

A similar methylation pattern is observed in diabetic conditions. Hypomethylation of TXNIP correlates with elevated expression and disrupted glucose homeostasis (Zhang *et al.*, 2017; Kim *et al.*, 2021).

The methylation status of the cg19693031 site within the TXNIP gene has been linked to fasting blood glucose regulation in non-diabetic Taiwanese adults (Tsai *et al.*, 2022). The relationship between TXNIP-cg19693031 DNA methylation (DNAm) and type 2 diabetes (T2D) is well-established, with strong correlations to HbA1c, insulin, and fasting glucose levels (Tsai *et al.*, 2022). Hypomethylation at TXNIP-cg19693031 has been robustly associated with T2D, as well

Corresponding authors
Email address: kkdutta@bsmrstu.edu.bd (Khokon Kumar Dutta)

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as elevated inflammatory biomarkers including VCAM-1, ICAM-1, MMP-2, sRAGE, and P-selectin. Notably, the connection between TXNIP-cg19693031 methylation and T2D persists independently of these inflammatory biomarkers (Xiang *et al.*, 2021).

Further studies have also demonstrated a marked decrease in methylation across five TXNIP loci in individuals with T2D compared to healthy controls, where increasing methylation levels correspond to a reduced T2D risk. Interactions among TXNIP methylation, obesity, and hypertriglyceridemia were identified as contributing factors to T2D onset (Zhang *et al.*, 2020).

Recent research has expanded on these findings, investigating how TXNIP methylation influences T2D risk in detail (Wu *et al.*, 2024; Maeda *et al.*, 2024). Two pivotal studies illustrate these associations, Wu *et al.* (2024) and Maeda *et al.* (2024) provide complementary insights into the role of TXNIP DNA methylation in type 2 diabetes (T2D) risk and glycemic regulation. Wu *et al.* (2024) in a nested case-control study, reported that higher methylation levels at TXNIP CpG sites 2–5 were associated with a 61–87% reduction in T2D risk, highlighting the protective potential of hypermethylation in this region. Similarly, Maeda *et al.* (2024) in a longitudinal study, found that hypomethylation at cg19693031 was linked to greater increases in fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) over four years, suggesting that hypomethylation may impair glucose regulation and serve as an early marker of diabetes risk. Together, these findings underscore the importance of TXNIP methylation in diabetes pathogenesis and risk prediction.

2. CRISPR-Cas technology for editing CpG methylation

The discovery of CRISPR-Cas9 system has opened the door and revolutionized genome editing (Doudna and Charpentier, 2014). The catalytically inactive form of dCas9 allows for precise epigenetic editing without altering DNA sequences. By fusing dCas9 to epigenetic effectors like methyltransferases or demethylases, scientists can manipulate CpG island methylation. This offers a potential therapeutic avenue for diseases such as diabetes, where aberrant CpG island methylation affects key genes like TXNIP.

Table 1. A timeline highlighting the key developments in the area of CRISPR-dCas9 Mediated CpG island methylation and demethylation.

Year	Key milestones and contributions
2013	CRISPR/Cas9 repurposed for targeted epigenetic modifications using dCas9 (Mali *et al.*, 2013; Maeder *et al.*, 2013).
2014	dCas9 fused with transcriptional regulators to control gene expression without DNA sequence alteration (Gilbert *et al.*, 2014).
2015	CRISPR/dCas9 fused with DNMT3A for site-specific CpG methylation, silencing genes, particularly in cancer research (Hilton *et al.*, 2015).
2016	Enhanced DNA methylation with dCas9 and multiple effectors, expanding applications in cancer research and stem cell differentiation (Xu *et al.*, 2016).
2017	dCas9 fused with TET1 for site-specific CpG methylation, reactivating silenced genes (Stepper *et al.*, 2017).
2018	Precise demethylation in endogenous genes, advancing research in neurodevelopmental disorders and cancer (Liu *et al.*, 2018)
2019	Enhanced specificity with dual-function dCas9 constructs for bidirectional CpG methylation control (Josipović *et al.*, 2019).
2020	Multiplexed control of multiple CpG islands, enabling studies of complex gene networks (McCarty *et al.*, 2020).
2021	Development of tools for fine-tuned methylation/demethylation with therapeutic potential in diseases involving aberrant methylation (Sapozhnikov *et al.*, 2021).
2022	Preclinical applications in neurological diseases and cancer; modulation of tumor suppressor genes using dCas9-methylation tools (Chen *et al.*, 2022).
2023	Focus on safer in vivo systems for targeted methylation and demethylation, addressing off-target effects (Vojta *et al.*, 2023).

3. Current research and future directions

Today, CRISPR/dCas9-based CpG island methylation and demethylation are being explored for treating diseases related to epigenetic dysregulation, such as cancer, neurological disorders, and metabolic diseases. Challenges remain in optimizing delivery, minimizing off-target effects, and achieving long-term, stable modifications (Cano-Rodriguez and Rots, 2016).

3.1 In Vivo examples of CRISPR-dCas9 mediated epigenetic editing

CRISPR/dCas9-mediated CpG island methylation and demethylation in vivo have shown potential in animal models for understanding gene regulation and exploring therapeutic applications. Some prominent examples are presented in Table 2.

Table 2. Key in vivo applications of CRISPR-dCas9-mediated epigenetic editing.

Target/Application	Study	Key findings	Significance
Targeting tumor/cancer related genes in cancer models	Braun *et al.* (2016)	Used CRISPR/dCas9 to activate and inactivate the cancer related genes in mice.	Demonstrated the potential to regulate the cancer related genes in vivo.
Manipulating memory-related genes in the brain	Liu *et al.* (2016)	A CRISPR/dCas9-TET1 fusion methylated CpG islands in the promoters of *Bdnf* in the adult mouse hippocampus. This increased expression of these genes, critical for memory formation and synaptic plasticity.	Showed that targeted demethylation can enhance gene expression in specific brain regions, suggesting potential treatments for neurodegenerative diseases or cognitive disorders.
Gene reactivation	Liu *et al.* (2018)	Used CRISPR/dCas9-TET1 to demethylate the FMR1 gene promoter in a Fragile X syndrome mouse model, leading to gene reactivation and partial phenotypic rescue.	Showcased the potential to treat genetic disorders characterized by epigenetic silencing.
Metabolism related gene targeting	Hanzawa *et al.* (2020)	Used CRISPR/dCas9-TET1CD and CRISPR/dCas9- SunTag to demethylate Fgf21 promoter both in vitro and in vivo.	Demonstrated the ability to edit metabolism related gene promoter through targeted epigenetic modifications.
Targeted repression of oncogenes in liver cancer	Senapedis *et al.* (2024)	CRISPR/dCas9-DNMT3A methylated CpG islands in the *Myc* promoter in a hepatocellular carcinoma mouse model. This reduced *Myc* expression, slowed tumor growth, and improved survival rates.	Demonstrated that targeted CpG methylation in oncogenes can suppress tumor growth, offering a potential therapeutic strategy for cancers with specific gene overexpression.
Epigenetic reversal of age-related memory decline	Swiech *et al.* (2015)	Used CRISPR/dCas9-TET1 to demethylate genes involved in synaptic plasticity in aged mice, improving cognitive function.	Showcased the potential to reverse age-related epigenetic changes and improve cognitive function.
Alzheimer's disease	Park *et al.* (2022)	Reduced expression of full-length APP and C99 in the DG of mouse brain.	Demonstrated the potential of CRISPR-dCas9-mediated epigenetic editing to target specific genes involved in Alzheimer's disease and reduce disease-related proteins.

4. CRISPR-dCas9-mediated reprogramming of TXNIP expression.

The CRISPR-dCas9 system can be leveraged to reprogram TXNIP expression by modifying its CpG island methylation status. For instance, CRISPR-dCas9-KRAB has been used to downregulate TXNIP by silencing its promoter region, reducing oxidative stress and improving glucose homeostasis. Alternatively, CRISPR-dCas9-TET1 can reprogram hypermethylated CpG islands in the TXNIP gene, leading to decreased TXNIP expression and improved insulin sensitivity.

5. Therapeutic potential of TXNIP reprogramming in diabetes

The ability to modulate TXNIP expression using CRISPR-dCas9 offers several therapeutic benefits for diabetes management. These include,
-Protecting pancreatic beta cells from apoptosis and oxidative stress.
-Improving insulin sensitivity in peripheral tissues.
-Enhancing glucose uptake and glycemic control.
-Reducing systemic inflammation associated with diabetes.

6. Conclusions

CRISPR-dCas9-mediated CpG island editing represents a novel and promising approach for diabetes treatment. By targeting key genes such as TXNIP, this technology has the potential to reverse hyperglycemia, enhance insulin sensitivity, and protect beta cells. While the potential is immense, further research is required to explore its therapeutic efficacy and address safety concerns.

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Ethical approval

No ethical approval is required for this study.

Declaration by authors

The authors' guidelines were used to generate the manuscript with the assistance of ChatGPT, an artificial intelligence program developed by OpenAI (which included the information mining, drafting and even for verification). However, the authors are responsible for the content and accuracy of the manuscript.

Data availability

The raw data are available in corresponding author and ready to submit when ask for it.

Informed consent statement

No informed consent was required to conduct the study.

Conflict of interest

The authors declare no conflict of interest.

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Authors' contribution

Khokon Kumar Dutta contributed to the design and writing of this review. The author critically reviewed the manuscript and agreed to submit final version of the article.

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