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REVIEW ARTICLE

The Role of Epigenetics in Association with Type 1 Diabetes

Kalina G. Mihova

Needham High School, 609 Webster St, Needham, MA, 02494, USA; kalinamihova07@gmail.com

ABSTRACT: Type 1 Diabetes (T1D) is an autoimmune disease that occurs when pancreatic β cells produce little or no insulin, thereby leading to an accumulation of glucose in the bloodstream and inability to process carbohydrates. In recent years, T1D has been increasingly researched due to the increased incidence of T1D. While genetics has been studied as a cause for T1D for decades, there have been new studies researching the role of epigenetics and environmental factors in association with T1D. Epigenetics is the study of gene expression and inheritance in which mechanisms such as DNA methylation, histone methylation, and non-coding RNA are used to silence and express specific genes. As understanding of epigenetics increases, there is a clearer correlation between epigenetics and autoimmune diseases. Despite the increase in knowledge on T1D, there is no cure for the disease, and more research will be required to elucidate the complete etiology of T1D and the role of epigenetics in T1D in its natural history. This systematic review describes the role of epigenetics and the environmental factors of maternal health, enteroviruses, age of food introduction, nitrate consumption, and psychological stress in T1D, and summarizes knowledge from current studies to aid in future research.

KEYWORDS: Biomedical and Health Sciences, Genetics and Molecular Biology, Disease Epigenetics, Type 1 Diabetes.

Introduction

Epigenetics:

Beginning in the 19th century, advances in embryology and cell biology led to an initial, broader definition of epigenetics. Up until the 1950s, epigenetics referred to the process by which the fertilized zygote passed on its traits. This definition later evolved to more specifically describe epigenetics as heritable changes in gene expression that are not expressed as changes in the DNA sequence.[1] Since "epi" refers to the above, the epigenome refers to the epigenetic marks layered over cells. These marks or epigenetic mechanisms are able to control whether a gene is expressed or silenced.[2]

Type 1 Diabetes:

Type 1 Diabetes (T1D) is an autoimmune disease in which the pancreatic β cells that produce insulin are destroyed (Figure 1). This destruction leads to hyperglycemia, a high concentration of glucose in the blood, since insulin facilitates the movement of glucose into the cells and stabilizes blood glucose levels.[3] This heightened concentration of glucose in the bloodstream causes weight loss, severe organ damage, heart failure, and early death.[4] In 1921, Frederick Banting discovered insulin and later made it available to the public. This discovery is still used as the primary treatment for T1D and has allowed diabetics to lead much longer and healthier lives. Although the exact causes of T1D and a cure for T1D have not yet been discovered, there have been numerous new technological advancements since the discovery of insulin to aid with insulin delivery.[5] Advancing clinical research and creating new treatments have gained increased focus as there has been a global increase in patients with T1D of about 3-4% in only the last 30 years, likely due to a combination of genetic and environmental factors.[6]

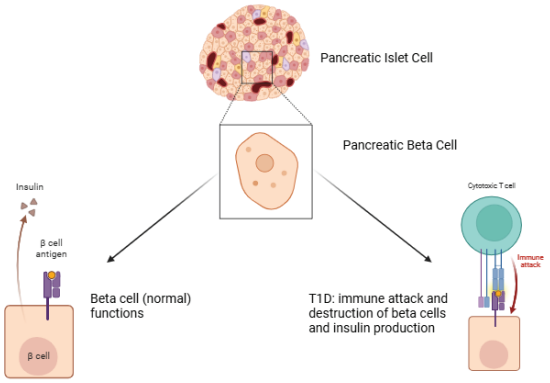

Figure 1: Figure 1 illustrates that pancreatic β cells are part of the pancreatic islet cells. On the left, there is a β cell of an individual without T1D. This cell can carry out regular functions, such as producing insulin and β-cell antigens, without any disturbances. In contrast, the right-hand side displays how a normal β cell may experience an immune attack in a person developing T1D. This immune attack then hinders the cell from carrying out regular functions, such as insulin production, and ultimately leads to an overall reduction in the number of β cells. (Created in BioRender.com)

New Diabetes Treatments:

T1D is commonly treated using continuous blood glucose monitors to measure blood sugar and insulin pumps or injections to stabilize blood glucose levels. These treatments are constantly being researched and improved upon to facilitate T1D management. For instance, one of the recently created treatments for T1D can delay the onset of diabetes by a couple of years. It does so by binding to an epitope of the CD3-epsilon chain expressed on mature T lymphocytes to manage the onset of immune system responses that occur in the development of the disease.[7] Another example of a new treatment is islet cell

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replacement therapy. In pursuing this therapy, embryonic stem cells offer a functional cure for patients of the disease by acting as pancreatic β cells and releasing insulin to regulate blood glucose levels. However, these replacement therapy options still face significant development challenges, and thus remain largely unavailable to patients and with relatively high patient risks and low adoption, where available, often in limited clinical or research settings.[8] As a result, there is an unmet need for treatments and cures for T1D.

Epigenetics in T1D:

Over the past 40 years, there has been mounting evidence that T1D can be caused by environmental factors.[5] There are over 60 susceptible genes for T1D, most of which are within the HLA region.[9] However, epigenetic changes in the immune system have been discovered in children prior to their development of T1D.[10] This means that some developments of T1D are likely caused by a prior disease and/or external environmental factors that lead to immune system disruption. The immune system then fails to attack accurately and instead damages the pancreatic β cells that produce insulin. Since disease, an external environmental factor, is hypothesized to lead to T1D, epigenetics may be involved.[11] That is because environmental factors, such as disease, use epigenetic mechanisms to express or suppress the underlying genes that factor into the islet cells' production of insulin. By looking at the current understanding of the connections between epigenetics and T1D, as well as recent treatments, we can more clearly understand the specific causes of T1D and use this information to inform ongoing research efforts.

Epigenetic mechanisms:

DNA methylation:

DNA methylation is an epigenetic mechanism involving the formation of a heritable mark created by a methyl group's covalent bond to the C5 position in the cytosine rings of DNA. The heritable mark caused by DNA methylation serves as a method of epigenetic silencing of transcription.[12]

Histone modifications:

Histone modifications regulate chromatin and transcription without expressing any change to the DNA sequence.[13] Histones are groups of proteins found in chromatin that act as a structure on which the DNA strands are tightly coiled. The expression of genes is repressed when the genes are bound by the histones and expressed when the DNA unwinds. This winding or unwinding occurs when epigenetic modifications change the charge of the histones and the DNA. Since the opposite charges of the histones and DNA keep the DNA wrapped (histones have a positive charge while DNA has a negative charge), changing the charge of one or both would also change the gene expression. There are nine different types of histone modification: acetylation, methylation, phosphorylation, and ubiquitylation are the most well-known modifications.[14]

Histone acetylation:

Histone acetylation occurs because histones are positively charged due to lysine and arginine. When acetylation neutralizes the lysine, the histones lose their positive charge and unwind from the DNA. As a result, histone acetylation increases gene expression because it allows for the expression of previously bound genes. This process of acetylation is catalyzed by histone acetyltransferases.[15]

Histone methylation and demethylation:

Histone methylation is the addition of methyl groups onto the histone protein. Histone methylation often prevents transcription factors from binding because it tightens histone tails around DNA, which decreases transcription. Histone demethylation, on the other hand, loosens the tails and leads to gene expression and an increase in transcription. This means that histone methylation can both activate and repress genes.[15]

Non-coding RNA:

Non-coding RNA (ncRNA) are functional RNA molecules that are not translated into protein. ncRNA regulates epigenetic mechanisms and controls the enzymes that catalyze processes such as DNA methylation, histone methylation and demethylation, and histone acetylation. NcRNA is important for understanding many autoimmune diseases because of its role in cell differentiation and tissue development.[16] NcRNA is also important to understanding autoimmune diseases because it is a component that leads to the immune system's attacking healthy tissue, which connects to how diseases attacking the pancreas are a potential cause of T1D.[17]

This up-to-date literature review will discuss the involvement of epigenetics in T1D and aim to provide a topic of discussion for future applications of epigenetics. Specifically, epigenetic and environmental factors such as the age of food introduction, consumption of nitrate, psychological stress, infancy, maternal health, and enteroviruses will be explored for their potential role in the development of T1D.

■ Discussion

Evidence of involvement of T1D with epigenetics:

Epigenetics is pointed out as a potential contributor to the development of T1D because evidence points to T1D not being attributed to genetic causes. Recent studies use the high discordance rate of monozygotic twins, known as MZ twins, in their development of T1D to prove the involvement of environmental factors. Since MZ twins come from the same fertilized egg and share 100% of their DNA, there must be environmental factors that are not part of the DNA sequencing that lead to only one twin developing the disease. Furthermore, the differences in incident rates of T1D between different countries also point to the involvement of environmental factors because there is no other explanation for such a rapid increase or such drastic differences. For instance, sub-Saharan Africa has an incidence rate of only 6% while parts of Scandinavia have a 77% incidence rate.[18] While many studies agree that this high percentage must be due to a common environmental trigger, this environmental trigger remains unclear.

Some possible environmental factors that could explain this difference in incidence rates are explored in the discussion and can be categorized as taking effect either before birth, during infancy, or post-infancy (Figure 2). While other environmental factors have been linked to the development of T1D, the diagram below represents a sample of environmental factors in each phase of development that have been identified with significant odds ratios in other literature.

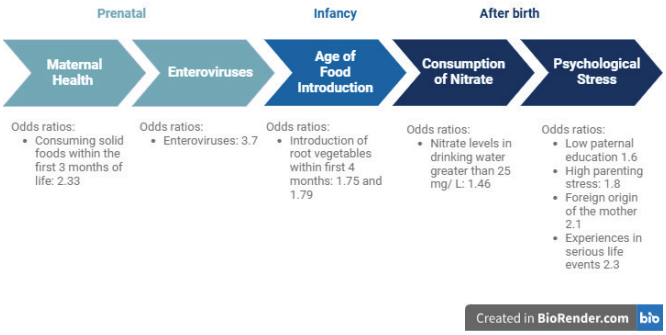

Figure 2: Figure 2 summarizes the main environmental factors associated with T1D included in the discussion. The figure categorizes the factors based on the stages of human development: prenatal, during infancy, or after birth. Odds ratios are included beneath each factor. (Created in BioRender.com)

Epigenetic and environmental factors associated with T1D:

Age of food introduction:

The development of T1D is potentially correlated with the age of food introduction, especially the introduction of root vegetables from an early age. For instance, the development of T1D, genetically, would be more likely with a certain human leukocyte antigen (HLA) system type since the HLA region is the region that is seen as predisposing a patient for T1D (there are 60 such regions). However, among siblings with different HLA types, the age of development is a more prominent factor than the HLA region type and predisposition.[18] Furthermore, studies have pointed to the early introduction of root vegetables, wheat, rye, oats, barley cereals, and eggs in the diet as potential risk factors for the development of T1D. One study has found that the early introduction of root vegetables in a child's diet, meaning in the first four months of life, leads to an increased risk of ß-cell autoimmunity among Finnish children. Children in the two groups that introduced root vegetables within the first four months experienced odds ratios of 1.75 and 1.79, where the baseline is 1. Therefore, the early introduction of root vegetables could be a contributor to the development of T1D.[19]

Consumption of nitrate:

Studies have shown a link between the consumption of toxins in food and water and the development of T1D. Specifically, nitrate and nitrosamine contamination in water is associated with an increase in T1D cases.[20] There have been conflicting studies in the Netherlands demonstrating that the correlation is only present for nitrate levels > 25 mg/ L.[21] When the nitrate levels in drinking water are greater than 25 mg/ L, there is an increased incidence ratio of 1.46, where the baseline level is 1. However, the study had a small sample size since only 15 out of the 1,064 were examined for this factor, which must be taken into account when judging the statistical significance of the data. Furthermore, a stronger correlation between drinking water with nitrate and the development of T1D was demonstrated in a study conducted in northern England. This study demonstrated a significant increase in patients as the nitrate in the water increased.[22]

Psychological stress:

Stress on β-cells is proven to negatively affect the immune response and lead to insulin resistance or the development of T1D. Factors such as rapid growth, trauma, and serious life events, such as the death of a family member, are all shown to increase the demand on β-cells.[23] An ABIS study with a baseline level of 1 demonstrates how physiological factors increase the odds ratios. For instance, high parenting stress leads to an odds ratio of 1.8, experiences in serious life events 2.3, foreign origin of the mother 2.1, and low paternal education 1.6.[24] This β-cell demand leads to non-functioning protein synthesis, proinsulin peptide degradation, and hybrid insulin peptide synthesis through transpeptidation, eventually triggering islet autoimmunity.[23]

Infancy and maternal health:

The development of T1D is potentially correlated with the early introduction of solid foods and the consumption of milk after infancy. A study examining the effects of breastfeeding on children of 3-12 months and the appearance of 4 types of islet antibodies found that an early introduction of solid food is associated with a higher risk of islet autoimmunity for children up to 3 years of age. For instance, the odds ratio for the development of T1D when consuming solid foods within the first 3 months of life is 2.33, where the baseline is 1.[25] Furthermore, a trial on the effects of frequent cow milk consumption found that elevated cow milk antibody concentrations and increased consumption of milk after infancy lead to a higher likelihood of developing islet autoimmunity.[26] In contrast, there has been no association discovered between maternal consumption of gluten, iron, and vitamin C and the risk of the child developing T1D.[27, 28] While maternal consumption of potential environmental factors does not highly impact the development of T1D, the consumption of solid foods during infancy and the consumption of milk after infancy are potential factors for the development of T1D.

Enteroviruses:

Enteroviruses have been researched for involvement in the destruction of pancreatic β cells and the development of T1D due to their ability to suppress immune responses. Enteroviruses are a group of single-stranded RNA viruses, such as the coxsackievirus. One study found that pancreatic β cells are prone to enterovirus infections that often destroy the cells. For instance, the Coxsackievirus B virus family was associated with T1D development due to its impact on the immune system.[29] A study measuring viral protein in the blood of pre-diabetes and diabetes patients found an odds ratio of 3.7, where the baseline is 1. This significant increase in the likelihood of developing T1D when an enterovirus infection is present means

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that there is an association between enteroviruses and the development of T1D.[30]

Current studies:

Epigenetics and its role in the development of T1D are increasingly being researched to discover causes for T1D. For instance, a study by Johnson *et al*. found 10 regions in the genome that differ between patients with T1D and people without the disease.[31] Furthermore, one study discovered that the methylation at the sites that are associated with the development of T1D can be detected years before the patient begins to develop the disease. This study identified specific autoantibodies and 88 CpG methylation sites that exhibit a correlation with the future onset of T1D, and therefore warrants further investigation.[32] As a result, it is now possible to use these 10 regions and specific site findings to screen patients who are at high risk of developing T1D to monitor or prevent these patients from developing the disease.

Conclusion

There is a rapid increase in patients with T1D, and novel treatments to delay the onset of T1D have been created. However, no permanent cure exists yet, and the exact causes for the disease remain unknown. Therefore, insight into potential epigenetic causes for T1D could aid in future research on the causes of T1D. It is hypothesized that environmental factors are associated with the development of T1D due to the high discordance rate of MZ twins and the genetically inexplicable increase in patients with T1D. Specifically, some environmental factors that could be contributors to the development of T1D are the age of food introduction, the consumption of nitrate, psychological stress, maternal health, and enteroviruses.

Future studies:

In the future, screening high-risk patients for pre-diabetes and researching environmental factors and epigenetic contributors can help lead to a better understanding of the complex etiology of T1D, which involves potentially heritable genetic factors, epigenetic conditions, and multiple intertwined epigenetic factors. Many other factors exist, such as cold climate, vitamin D deficiency, pollution and heavy metal exposure, toxin exposure, childhood obesity, and the gut microbiome, that should be considered in the future. In addition, while this study looks at these factors in isolation, it provides an important jumping-off point for these factors to be studied concurrently in real-world settings, which will help improve understanding of each factor's contribution. Furthermore, since T1D is associated with DNA methylation and histone modification, the creation of epigenetic treatments for T1D is plausible. For instance, histone modification inhibitors function as epigenetic treatments for cancer and therefore have great potential as future therapeutic, or even curative, interventions for T1D that merit future research.

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References

1. Jerram ST, Dang MN, Leslie RD. The Role of Epigenetics in Type 1 Diabetes. Curr Diab Rep. 2017;17(10):89.
2. Riggs AD. X inactivation, differentiation, and DNA methylation. Cytogenet Cell Genet. 1975;14(1):9-25.
3. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391(10138):2449-62.
4. Siang Yong Tan JM. Frederick Banting (1891-1941): Discoverer of Insulin. Singapore Medical Journal. January 2017.
5. Atkinson MA. The pathogenesis and natural history of type 1 diabetes. Cold Spring Harb Perspect Med. 2012;2(11).
6. Norris JM, Johnson RK, Stene LC. Type 1 diabetes-early life origins and changing epidemiology. Lancet Diabetes Endocrinol. 2020;8(3):226-38.
7. Vertex Announces Positive Results From Ongoing Phase 1/2 Study of VX-880 for the Treatment of Type 1 Diabetes Presented at the American Diabetes Association 84th Scientific Sessions [press release]. Vertex Pharmaceuticals IncJune 21, 2024.
8. Ramos EL, Dayan CM, Chatenoud L, Sumnik Z, Simmons KM, Szypowska A, *et al*. Teplizumab and beta-Cell Function in Newly Diagnosed Type 1 Diabetes. N Engl J Med. 2023;389(23):2151-61.
9. Xie Z, Chang C, Huang G, Zhou Z. The Role of Epigenetics in Type 1 Diabetes. Adv Exp Med Biol. 2020;1253:223-57.
10. Zhang J, Chen LM, Zou Y, Zhang S, Xiong F, Wang CY. Implication of epigenetic factors in the pathogenesis of type 1 diabetes. Chin Med J (Engl). 2021;134(9):1031-42.
11. Al Aboud NM, Tupper C, Jialal I. Genetics, Epigenetic Mechanism. StatPearls. Treasure Island (FL)2024.
12. Jin B, Li Y, Robertson KD. DNA methylation: superior or subordinate in the epigenetic hierarchy? Genes Cancer. 2011;2(6):607-17.
13. Alaskhar Alhamwe B, Khalaila R, Wolf J, von Bulow V, Harb H, Alhamdan F, *et al*. Histone modifications and their role in epigenetics of atopy and allergic diseases. Allergy Asthma Clin Immunol. 2018;14:39.
14. Greer EL, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet. 2012;13(5):343-57.
15. Lee HT, Oh S, Ro DH, Yoo H, Kwon YW. The Key Role of DNA Methylation and Histone Acetylation in Epigenetics of Atherosclerosis. J Lipid Atheroscler. 2020;9(3):419-34.
16. Pathania AS. Crosstalk between Noncoding RNAs and the Epigenetics Machinery in Pediatric Tumors and Their Microenvironment. Cancers (Basel). 2023;15(10).
17. Kumar D, Sahoo SS, Chauss D, Kazemian M, Afzali B. Non-coding RNAs in immunoregulation and autoimmunity: Technological advances and critical limitations. J Autoimmun. 2023;134:102982.
18. Akil AA, Jerman LF, Yassin E, Padmajeya SS, Al-Kurbi A, Fakhro KA. Reading between the (Genetic) Lines: How Epigenetics is Unlocking Novel Therapies for Type 1 Diabetes. Cells. 2020;9(11).
19. Virtanen SM, Takkinen HM, Nevalainen J, Kronberg-Kippila C, Salmenhaara M, Uusitalo L, *et al*. Early introduction of root vegetables in infancy associated with advanced ss-cell autoimmunity in young children with human leukocyte antigen-conferred susceptibility to Type 1 diabetes. Diabet Med. 2011;28(8):965-71.
20. Moltchanova E, Rytkonen M, Kousa A, Taskinen O, Tuomilehto J, Karvonen M, *et al*. Zinc and nitrate in the ground water and the incidence of Type 1 diabetes in Finland. Diabet Med. 2004;21(3):256-61.
21. van Maanen JM, Albering HJ, de Kok TM, van Breda SG, Curfs DM, Vermeer IT, *et al*. Does the risk of childhood diabetes mellitus require revision of the guideline values for nitrate in drinking water? Environ Health Perspect. 2000;108(5):457-61.
22. Parslow RC, McKinney PA, Law GR, Staines A, Williams R, Bodansky HJ. Incidence of childhood diabetes mellitus in York-

shire, northern England, is associated with nitrate in drinking water: an ecological analysis. Diabetologia. 1997;40(5):550-6.
23. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. Lancet. 2016;387(10035):2340-8.
24. Sepa A, Wahlberg J, Vaarala O, Frodi A, Ludvigsson J. Psychological stress may induce diabetes-related autoimmunity in infancy. Diabetes Care. 2005;28(2):290-5.
25. Hakola L, Takkinen HM, Niinisto S, Ahonen S, Nevalainen J, Veijola R, *et al*. Infant Feeding in Relation to the Risk of Advanced Islet Autoimmunity and Type 1 Diabetes in Children With Increased Genetic Susceptibility: A Cohort Study. Am J Epidemiol. 2018;187(1):34-44.
26. Niinisto S, Cuthbertson D, Miettinen ME, Hakola L, Nucci A, Korhonen TE, *et al*. High Concentrations of Immunoglobulin G Against Cow Milk Proteins and Frequency of Cow Milk Consumption Are Associated With the Development of Islet Autoimmunity and Type 1 Diabetes-The Trial to Reduce Insulin-dependent Diabetes Mellitus (IDDM) in the Genetically at Risk (TRIGR) Study. J Nutr. 2024;154(8):2493-500.
27. Mattila M, Hakola L, Niinisto S, Tapanainen H, Takkinen HM, Ahonen S, *et al*. Maternal Vitamin C and Iron Intake during Pregnancy and the Risk of Islet Autoimmunity and Type 1 Diabetes in Children: A Birth Cohort Study. Nutrients. 2021;13(3).
28. Hakola L, Lund-Blix NA, Takkinen HM, Tapanainen H, Niinisto S, Korhonen TE, *et al*. Maternal gluten, cereal, and dietary fiber intake during pregnancy and lactation and the risk of islet autoimmunity and type 1 diabetes in the child. Clin Nutr ESPEN. 2024;62:22-7.
29. Sarah J Richardson NGM. Enteroviral infections in the pathogenesis of type 1 diabetes: new insights for therapeutic intervention. Curr Opin Pharmacol. December 2018.
30. Yeung WC, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies. BMJ. 2011;342:d35.
31. Johnson RK, Vanderlinden LA, Dong F, Carry PM, Seifert J, Waugh K, *et al*. Longitudinal DNA methylation differences precede type 1 diabetes. Sci Rep. 2020;10(1):3721.
32. Stefan M, Zhang W, Concepcion E, Yi Z, Tomer Y. DNA methylation profiles in type 1 diabetes twins point to strong epigenetic effects on etiology. J Autoimmun. 2014;50:33-7.

Author

Kalina Mihova is a junior at Needham High School, MA. Kalina has been living with T1D since 2017 and is passionate about clinical research. Kalina is a Level 9 rhythmic gymnast and is involved with piano and debate. She is interested in pursuing biology or genetics at a leading university.

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