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Research Progress of Alternative Polyadenylation in Diseases Related to Glycolipid Metabolism

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Abstract: With changes in lifestyle, sedentary behavior or lack of physical exercise increases the risk of various glycolipid metabolic disorders. Glycolipid metabolic dysregulation refers to abnormalities in the metabolism of carbohydrates and lipids, including diseases such as diabetes, obesity, and metabolic syndrome. In-depth research into the molecular mechanisms of glycolipid metabolic dysregulation can help develop more effective treatment strategies and preventive measures to prevent the occurrence of long-term complications such as cardiovascular diseases. Alternative polyadenylation (APA) is an important form of RNA modification that helps regulate gene expression and generate protein diversity. This modification can affect processes such as RNA stability, post-transcriptional modification, and translational regulation. Recent studies have confirmed that APA can influence the expression of genes involved in glucose and lipid metabolism, increasing the probability of developing immune, endocrine, and metabolic diseases. The review explains the research progress of APA involvement in various metabolic diseases and explores these mechanisms, providing new insights and directions for novel metabolic disorder treatment strategies.

Keywords: APA, alternative polyadenylation, glycolipid metabolic diseases, 3'UTRs, diabetes, obesity, metabolism, dysfunction

Introduction

Alternative polyadenylation (APA), a prevalent phenomenon in eukaryotes, aids in regulating gene expression and generating protein diversity. It is estimated that 30% to 70% of genes produce mRNA isoforms with multiple optional 3' Untranslated Regions (3'UTRs).[1] APA plays a critical role in development, and its misregulation is associated with various human diseases, including cancer.[2] APA is mainly divided into two types: 3'UTR APA and intronic APA (IPA). 3'UTR-APA mainly affects the stability of mRNA, translation efficiency, nuclear output and cell localization, while IPA may lead to the change of coding sequence, thus affecting the function and stability of protein.[3] The APA modification of mRNA has emerged as a crucial mechanism in post-transcriptional gene regulation in higher eukaryotes, wherein processes involving poly(A) influence translation, mRNA stability, nuclear export, and play significant roles in various physiological and pathological processes[4]. With changes in lifestyle, prolonged sedentary behavior or lack of physical exercise increases the risk of various metabolic disorders, such as type 2 diabetes, obesity, cardiovascular diseases, non-alcoholic fatty liver disease, high cholesterol levels, and others. Additionally, there is a growing trend towards younger onset of these conditions, posing a serious threat to human health.[5] Timely treatment of metabolic pathway dysregulation may improve the development of metabolic-related diseases such as diabetes and obesity,[6] If the above-mentioned diseases are not treated properly, they may lead to various chronic complications throughout the body.[7] APA dysregulation is associated with various metabolic pathways, with the most extensively studied being abnormalities in carbohydrate and lipid metabolism. Research indicates that APA serves as a pathogenic factor in multiple diseases, including neonatal diabetes, type 1 diabetes, type 2 diabetes, and preeclampsia.[8,9] Additionally, APA can influence the expression

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of genes involved in glucose and lipid metabolism, thereby increasing the likelihood of immune, endocrine, and metabolic diseases.[10] This discovery suggests that APA may potentially alter metabolic homeostasis through modifications to metabolism-related genes, thereby playing a role in disease progression.

The relationship between alternative polyadenylation and metabolic dysregulation is an active area of research, with studies steadily increasing in recent years (see Figure 1). However, the mechanisms underlying APA involvement in metabolic-related diseases still require further investigation for clarification. Exploring these mechanisms can provide new insights and directions for novel therapeutic strategies aimed at metabolic disorders.

Alternative Polyadenylation and Its Mechanisms Impacting Metabolic Dysregulation

Overview of Alternative Polyadenylation

For eukaryotes, APA is a necessary step in mRNA maturation, determining mRNA stability, localization, translation, and protein functionality. Moreover, APA plays an important role in the diversity of mRNA subtypes. The formation of multiple mRNA subtypes can enhance the diversity and complexity of the transcriptome and affect the expression of miRNA in mRNA. Combined with the potential downstream effects of regulatory and alternative splicing events,[11] the resulting mRNA isoforms differ in the length of their coding DNA sequence (CDS) or 3' UTR, a process that contributes to proteomic diversity and fine-tuning gene expression,[12] The length of 3' UTR can affect the expression of proteins,[13] and the distance of the PolyA site from CDS determines the length of the 3' UTR; As an important regulatory mechanism of gene expression, many factors can influence the process of APA, primarily including cis-regulatory elements and trans-acting factors. Additionally, environmental changes, stress, and metabolic adaptations during development can also induce APA in gene subgroups.[3] It is generally believed that APA occurs synchronously, meaning RNA selects multiple polyadenylation sites simultaneously. However, in a recent study, some scholars proposed that APA might occur sequentially.[14] In simple terms, it means that after undergoing polyadenylation once, an RNA molecule undergoes multiple polyadenylations at different sites, enriching the diversity and complexity of the transcriptome. This process affects mRNA stability, translation efficiency, and changes in protein expression.

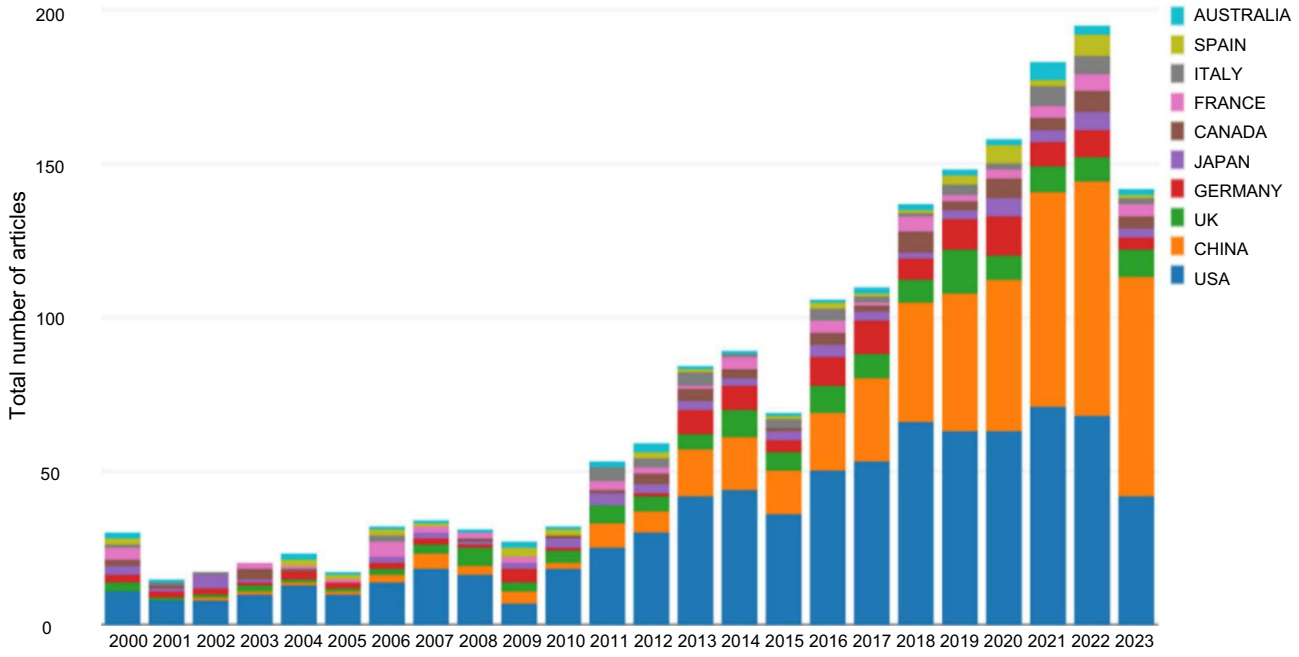

Figure 1 Changes in the number of articles on APA in the field of metabolism over the years.

In this study on glycolipid metabolic dysregulation, APA has been identified as one of the key factors contributing to metabolic disorders. Further explanations on the progress of APA modification studies of different metabolism-related genes have been provided from the perspectives of various metabolic diseases (refer to Figure 2). Understanding the regulatory mechanisms of metabolism and the mechanisms underlying the occurrence of related diseases can aid in formulating prevention and treatment strategies to maintain a healthy metabolic state.

Glucose Metabolism and Alternative Polyadenylation

Imbalances in glucose metabolism and its regulation can lead to metabolic diseases such as insulin resistance type 2 diabetes and metabolic syndrome.[15] These disorders are characterized by impaired insulin signaling and impaired glucose uptake and abnormal glucose production, which in turn lead to abnormal blood sugar levels and an increased risk of cardiovascular disease.[16]

A study found that the mRNA of a novel high-glucose-regulated gene 14 (HGRG-14) in human mesangial cells cultured in 30mM d- glucose for 21 days was regulated after transcription.The mRNA of long subtype HGRG-14 was increased in high glucose environment. This form has a long 3' untranslated region, including several destabilization sequences of ATTTA RNA, with short half-life and decreased protein level.[17] The GLUT4 gene in chickens produced at least 14 transcripts through APA, predicting the empty expression of 12 amino acid sequences, indicating that GLUT4 was mainly expressed in pectoralis major leg muscles and myocardium, and mRNA levels fluctuate significantly with the development of pectoralis and leg muscles in birds.[18] Through samples collected from four insulin-expressing tissues in rats (including adult and fetal pancreas, yolk sac, and insulinoma cell lines), it was found that the proinsulin mRNA transcripts from insulinoma cell lines and fetal pancreatic tissues were estimated to be 100 and 50 bases longer,

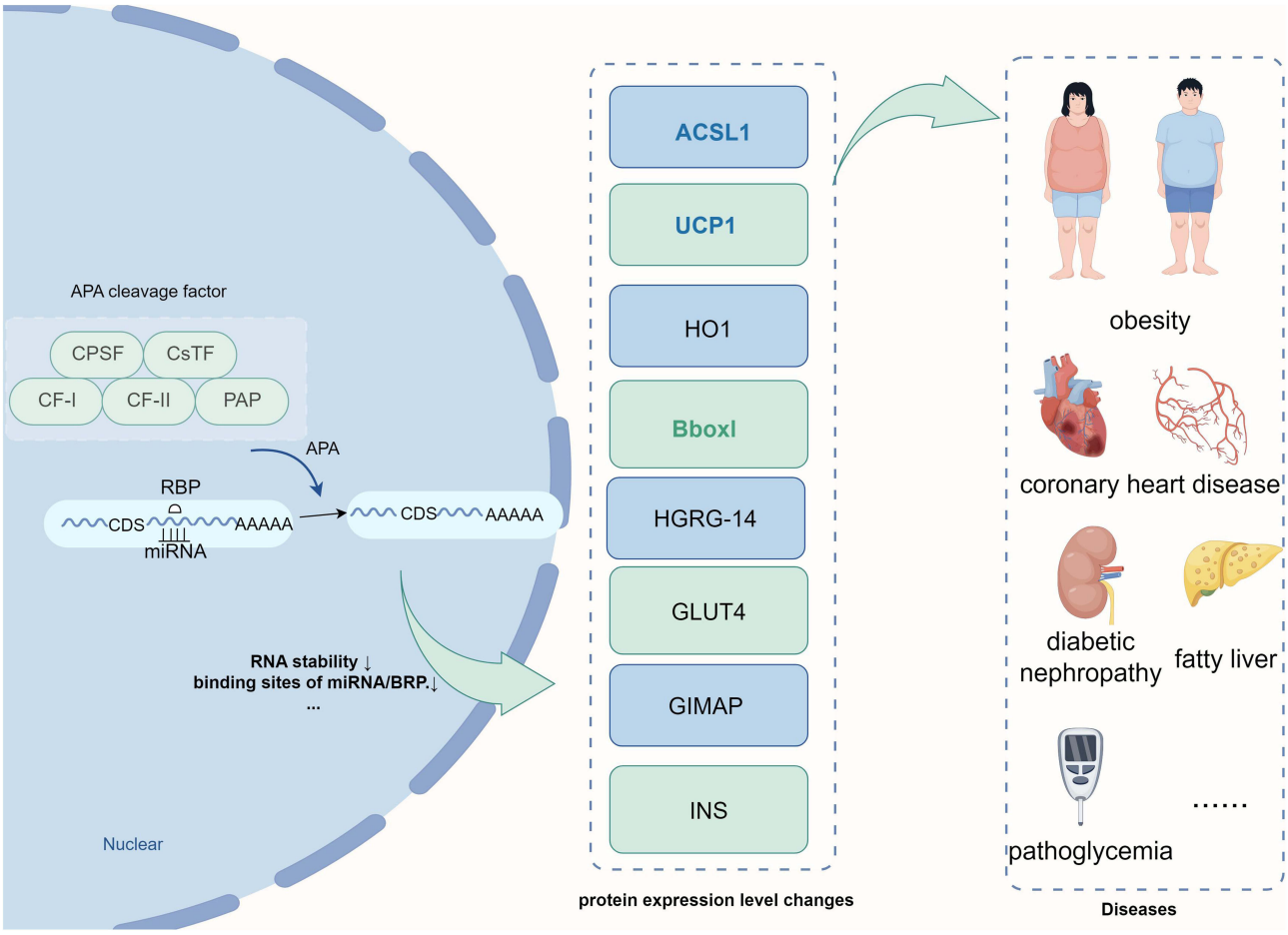

Figure 2 Research progress of APA modification in metabolic diseases. By Figdraw.

respectively, than those from adult rat pancreas. The differences in length observed could be explained by variations in 3'-polyadenylation. However, proinsulin mRNA did not exhibit any polyadenylation regulation under conditions where mRNA levels varied from low to high in treated animals. The role of polyadenylation of proinsulin mRNA in the physiological regulation of insulin biosynthesis remains unclear.[19]

APA may affect insulin sensitivity and glucose uptake and transport by influencing the changes in mRNA isoforms of genes related to insulin, glucose regulation, and transport. This, in turn, affects the interaction between sugar metabolism and glucose metabolism.

Lipid Metabolism and Alternative Polyadenylation

Lipid metabolism plays a critical role in maintaining energy balance, cellular structure and function, hormone synthesis, and various other physiological processes. Dysregulation of lipid metabolism can lead to the development of various diseases such as hypercholesterolemia, hyperlipidemia, and atherosclerosis. These conditions can result in lipid deposition within blood vessels and damage to arterial walls, increasing the risk of cardiovascular diseases.[20]

Uncoupling protein 1 (UCP1) is a proton channel located in the inner mitochondrial membrane, utilized to dissipate proton gradients and uncouple the electron transport chain to generate heat rather than adenosine triphosphate. The 3'-UTR of Ucp1 mRNA undergoes differential processing between mice and humans, quantitatively affecting UCP1 synthesis and heat production.[21]

Heme oxygenase 1 (HO1) exerts inhibitory effects on preadipocyte differentiation. HO1 with long 3'UTR variants has been identified as a direct target of miR155-5P and miR377-3P. By escaping microRNA inhibition, the short variant of HO1 3'UTR generated by APA exhibits higher expression levels. Therefore, in murine embryonic fibroblast 3T3-L1 cells, the inhibitory effect of the short subtype of HO1 3'UTR on preadipocyte differentiation is stronger than that of the long subtype.[22] Acyl-CoA synthetase 1 (ACSL1) is a crucial subtype of the ACSL family involved in the synthesis of acyl-CoA lipids and the oxidation of fatty acids. Alternative polyadenylation leads to two transcripts of the ACSL1 gene, which are translated into ACSL1-a and ACSL1-b. Overexpression of ACSL1-a promotes the synthesis of intracellular diacylglycerol, while ACSL1-b facilitates the synthesis of triglycerides. Transfection of ACSL1 shRNA significantly reduces the levels of both transcripts and induces a notable decrease in triglyceride content following differentiation.[23] L-carnitine is a key molecule in mitochondrial and peroxisomal lipid metabolism. It is biosynthesized from gamma-butyrobetaine by gamma-butyrobetaine hydroxylase (Bbox1). In the liver of rats, four alternatively polyadenylated forms of Bbox1 mRNA have been identified. The maturation of Bbox1 mRNA is subject to nutritional regulation in the liver through a process of selective polyadenylation, which regulates L-carnitine biosynthesis to provide energy.[24]

Other Metabolic Pathways

Apart from its involvement in major glucose and lipid metabolism, APA may also impact metabolic pathways and mitochondrial functions during mRNA maturation, leading to disruptions in energy metabolism. In APA, there may be alterations in metabolic pathways associated with normal mRNA maturation processes. This includes abnormalities in later steps such as RNA splicing, modifications, and polyadenylation. These changes may also manifest as shifts in metabolic pathways from oxidative phosphorylation to glycolysis in certain diseases.[25–27]

Various studies indicate that APA may play a role in the dysregulation of glucose and lipid metabolism through several mechanisms, including gene expression regulation, modulation of insulin signaling pathways, lipid metabolism regulation, and transcriptional regulation. APA can alter the expression levels of glucose and lipid metabolism-related genes by selecting different polyadenylation sites, leading to the generation of mRNA isoforms with different 3' UTRs. Through regulatory elements contained in different isoforms, such as microRNA binding sites or stability elements, APA can influence mRNA stability, translation efficiency, and protein expression, ultimately affecting genes related to glucose and lipid metabolism (see Table 1).

Metabolic Diseases and Alternative Polyadenylation

During mRNA maturation, APA maintains the transcription of normal genetic information under the joint action of various factors. This precise process involves multiple regulatory factors such as transcription factors, RNA-binding

Table 1 APA Changes of Metabolism-Related Indicators

Gene	Metabolic Type	Species	Regional Variations of 3' UTR	Relevance to APA	Role	Reference
HGRG-14	Sugar metabolism	Human	Prolong	High glucose conditions acutely affect the processing of HGRG-14 mRNA, reducing its half-life and lowering protein levels.	May have significant effects on cell function and be a contributory factor in the mechanism leading to diabetic nephropathy in vivo	[17]
GLUT4	Sugar metabolism	Chicken	Generate at least 14 transcripts	The mRNA levels fluctuate significantly during the development of avian myocardium, pectoral muscles, and leg muscles, allowing the prediction of coding for 12 amino acid sequences.	Regulating insulin-mediated glucose homeostasis in mammals	[18]
Proinsulin	Sugar metabolism	Mice	The transcripts of fetal mice are estimated to be 100 and 50 bases larger than those of adults.	The role in physiological regulation remains unclear.	-	[19]
UCP1	Lipid metabolism	Mice	Shorten	The 3'-UTR of mRNA undergoes differential processing between mice and humans, which can quantitatively affect UCP1 synthesis and thermogenesis.	Dissipate the proton gradient and uncouple the electron transport chain to generate heat instead of adenosine triphosphate.	[21]
HO1	Lipid metabolism	Mice	Shorten	The short subtype of HO1 3'UTR exhibits a stronger inhibitory effect on preadipocyte differentiation compared to the long subtype of HO1 3'UTR.	A stronger inhibitory effect on the preadipocyte differentiation	[22]
ACSL1	Lipid metabolism	Human	The two subtypes have different functions	Overexpression of ACSL1-a promotes the synthesis of intracellular diacylglycerol, while ACSL1-b facilitates the synthesis of triglycerides.	Triglyceride synthesis process	[23]
Bbox1	Lipid metabolism	Mice	4 subtypes	The maturation of Bbox1 mRNA is regulated by a process of selective polyadenylation in the liver, which is nutritionally regulated, to modulate carnitine biosynthesis for energy provision.	Nutritionally regulated in the liver	[24]

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proteins, and RNA modification enzymes. From the perspective of partial APA-related pathogenic genes, it has been discovered that variants in conserved polyA+ signal sequences can alter the length of 3'UTRs and the stability of IRF5 mRNA,[28] indicating a correlation between 3' UTR length and APA factor expression levels. Large-scale population genetic investigations have revealed numerous genetic variations that may affect APA,[29] thereby influencing disease susceptibility and phenotypic diversity. APA leads to various metabolic diseases and the resulting specific genotypic variations (see Table 2).

In general, APA commonly leads to the occurrence of tumors, blood disorders, and immune diseases. However, the abnormal APA causing metabolic diseases has emerged as a direction requiring further attention in recent years, and it is the focal point of this discussion. APA in the field of metabolism is a particular area of interest for researchers worldwide, as evidenced by the research trends in various metabolic disease areas. This further emphasizes the importance of APA in understanding and addressing metabolic health issues. These studies not only contribute to our understanding of the mechanisms behind metabolic diseases but also provide valuable insights for future prevention and treatment strategies.

Diabetes

Research has found that under the influence of mutations in the GTPase immune-associated protein (GIMAP), the APA process in mice is disrupted, making them more susceptible to type 1 diabetes.[30] Neonatal diabetes is a rare condition of unknown etiology that can manifest within a period after birth, generally caused by single-gene mutations. In the neonatal population, mutations abolishing the polyadenylation signal in the 3' UTR lead to severe RNA instability, while mutations affecting the start codon result in reduced transcription of the proinsulin gene,[32] Disruption of insulin biosynthesis may occur, ultimately resulting in the onset and progression of neonatal diabetes. Loss of insulin-degrading enzyme (IDE) in mice leads to the accumulation of brain β-amyloid (Abeta), hyperinsulinemia, and impaired glucose tolerance.

In particular, genetic linkage and allele variants are associated with the reduced function of IDE in type 2 diabetes. Studies have identified six different human IDE transcripts, with most differences attributed to alternative polyadenylation sites[31] The targeting of two subtypes of organelles depends on which of the two translation initiation sites is utilized, and only those utilizing the second site regulate the secretion of Abeta. This may provide new directions for identifying mutations predisposing patients to diabetes. Under hyperglycemic conditions, the extension of the 3'UTR in genes of diabetic nephropathy patients increases protein expression levels without increasing mRNA expression levels. This may enhance protein translation by altering the binding sites of RNA-binding proteins.[13]

Non-Alcoholic Fatty Liver Disease

The early stage of nonalcoholic fatty liver disease (NAFLD) is related to the defect of pre-mRNA processing, and the defect of polyadenylation may be the basis of the imbalance of key metabolic genes in the liver. It was found that NAFLD was related to the significant decrease of splicing factor 10 (SRSF10) rich in serine and arginine, and SRSF10 prevented the interaction between mRNA polyadenylation mechanism and intron polyadenylation site. The weight of AAV-Srsf10-kd mice increased slightly when fed with high-fat diet, and the inactivation of SRSF10 was related to the significant damage of glucose tolerance and insulin sensitivity. Srsf10-kd mice showed steatosis and direct quantitative increase of triglyceride content in liver. In addition, the increase of steatosis is related to the increase of lipid droplet size and liver/body weight ratio. After inactivation of SRSF10, peroxisome proliferator-activated receptor alpha (PPARα) was significantly down-regulated, in addition, PPARα targets such as liver factor Fgf21 and lipolytic factor Ehhadh were significantly reduced. In a word, the inactivation of SRSF10 leads to the imbalance of key metabolic genes such as PPARA polyadenylation, which aggravates the metabolic dysfunction induced by diet.[33]

Obesity

Obesity is one of the most common metabolic disorders and is also an independent risk factor for other diseases such as diabetes, hypertension, and certain cardiovascular diseases. Typically, obesity is associated with an increase in adipocytes and the accumulation of inflammatory factors. Changes in RNA modifications may affect intracellular signaling pathways, including the production and effects of cAMP. Moreover, the activation of A1 adenosine receptors in adipocytes can reduce adenylate cyclase and cAMP levels,[37] thereby inhibiting lipolysis. Some transcription factors may play

Table 2 Metabolic Diseases Associated with APA

Disease	Relevance of APA	Gene	Metabolic Type	Role	Reference
Type 1 Diabetes	The single nucleotide polymorphism (SNP) in the 3'UTR region of the GIMAP5 gene is associated with an increase in IA-2 (insulinoma-associated antigen-2) autoantibodies in patients with type 1 diabetes.	GIMAP	Glucose metabolism abnormalities are predominant.	Apoptosis in T cells	[30]
Type 2 Diabetes	The replacement polyadenylation site results in the loss of the insulin-degrading enzyme	IDE	Glucose metabolism abnormalities are predominant.	Accumulation of cerebral amyloid beta-protein (Abeta), hyperinsulinemia, and glucose intolerance	[31]
Neonatal diabetes mellitus	Abolishing the 3' UTR mutation of the polyadenylation signal leads to severe instability of the RNA	Heterozygous missense mutation in the coding region of the INS gene.	Glucose metabolism abnormalities are predominant.	Beta-cell death through endoplasmic reticulum stress and apoptosis	[32]
Diabetic nephropathy	The 3'UTR APA of the gene may have altered the binding site of the RNA-binding protein, thereby enhancing protein translation	CYB5R1,PDLIM1, PDCD6,MYOF and CFH	Glucose metabolism abnormalities are predominant.	APA genes were enriched in inflammation-related biological processes	[13]
Non-alcoholic fatty liver disease	Inactivation of SRSF10 results in polyadenylation of PPARA	PPARA	Lipid metabolism abnormalities are predominant.	Exacerbate diet-induced metabolic dysfunction	[33]
Obesity	Genes with multiple APA loci are encoded by APA expression sequences or 3 UTR distinct mRNA subtypes	Ccdc25, Dtd2, Gm14403, Hlf, Lyrm7, Mrpl3, Pisd-ps3, Sbsn, Slx1b, Spon	Lipid metabolism abnormalities are predominant.	Provide insights into the relationship between PA and the hypothalamus in the context of obesity	[34]
Familial hypercholesterolemia	RNA structure motifs bind to interacting molecules, leading to alternative exon/intron recognition, polyadenylation, and further disease progression.	-	Lipid metabolism abnormalities are predominant.	Improve lipid profile	[35]
Intestinal disease X-linked syndrome (IPEX syndrome)	The rare A-to-G PAS mutation in the FOXP3 gene (from AAUAAA to AAUGAA) leads to the degradation of the FOXP3 transcript, resulting in decreased FOXP3 expression.	FOXP3 gene (AAUAAA→AAUGAA)	Glucose metabolism abnormalities are predominant.	Causal of IPEX in this family by a mechanism of nonspecific degradation of the FOXP3 gene message	[36]
Osteoarthritis	The polyadenylation site (COL3-APS) is upregulated in osteoarthritis samples, which may indicate APA variations. However, its correlation remains contradictory in other studies and requires further discussion.	-	Metabolic shift to predominance	This finding differentiates knee osteoarthritis from pathologies such as cancer where APA is more commonly observed.	[26,27]

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a regulatory role in the occurrence of selective adenylation events, influencing the 3' end processing of specific mRNA. In some studies, DNA methylation, by recruiting gene silencing proteins or inhibiting the binding of transcription factors,[38] can induce the organism into a state of chronic metabolic disease. This can ultimately lead to dysregulation of lipid metabolism, resulting in the occurrence and development of obesity and related diseases. After an 11-week high-fat diet, APA sites in the hypothalamus of two distinct multi-gene obesity (fat line) and healthy lean (lean line) mouse models were measured. Seventeen target genes with differentially expressed isoforms were identified.[34] In addition, mRNA levels of preproendothelin-1 (ppET1) and endothelin receptor type B (endothelin receptor type B) genes are significantly upregulated in the liver tissue of obese patients,[39] indicating a potential correlation between obesity and liver disease at the level of gene modulation.

Familial Hypercholesterolemia

In a study, it was found that changes in the 3'UTR of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) are associated with interactions with miR-4721 and miR-564, affecting the occurrence and development of familial hypercholesterolemia patients.[35]

Intestinal Disease X-Linked Syndrome

Intestinal X-linked syndrome is an endocrine disorder associated with various manifestations such as dermatitis, enteropathy, type 1 diabetes, thyroiditis, and others.,[40] In patients with intestinal X-linked syndrome, a mutation occurs in the first polyadenylation signal after the stop codon, changing AAUAAA to AAUGAA. This mutation leads to aberrant polyadenylation processes and ultimately results in X-linked monogenic immune dysregulation.[36]

Osteoarthritis

Osteoarthritis (OA) is a non-inflammatory degenerative joint disease characterized by mild inflammation and metabolic dysfunction.[25] In one study, five different RNA isoforms of collagenase-3 were detected, among which the polyadenylation site (COL3-APS) was upregulated in samples from osteoarthritis patients.,[26] However, the mechanisms underlying the association of osteoarthritis with APA are not yet fully understood, as some studies have indicated that osteoarthritis does not cause widespread changes in the usage of its polyadenylation sites.[27] The mechanism related to osteoarthritis needs to be further improved.

Conclusion and Future Perspective

APA, as a regulatory mechanism, generates multiple mRNA isoforms by selecting different polyadenylation sites within genes. APA can influence gene expression patterns, mRNA stability, and translation efficiency, potentially impacting various cellular processes, including glucose and lipid metabolism. APA may alter insulin sensitivity and glucose uptake and transport by affecting the mRNA isoforms of genes involved in insulin and glucose regulation and transport, thereby influencing glucose metabolism in glucose metabolism. APA can also affect lipid metabolism by regulating the expression of genes involved in lipid synthesis, transport, and oxidation. In metabolic disorders, there is relatively more attention on APA mechanisms concerning obesity, while the field of APA research is still evolving, requiring further studies to fully understand the mechanisms and consequences of APA in metabolic disorders.

In summary, APA, as a potential regulatory mechanism, can influence glucose and lipid metabolism by modulating gene expression patterns and mRNA processing. The regulation of metabolic diseases by APA may serve as a potential biological target for diagnosis and treatment. However, more research is needed to elucidate the exact mechanisms and functional significance of APA in metabolic disorders.

Statement

During the preparation of this work the authors used ChatGPT in order to Translate part of the article. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Statement of Ethics

This article does not contain any studies with human or animals performed by any of the authors.

Consent for Publication

Agreed to publish.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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