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REVIEW

The Role of Uridine in Health and Disease

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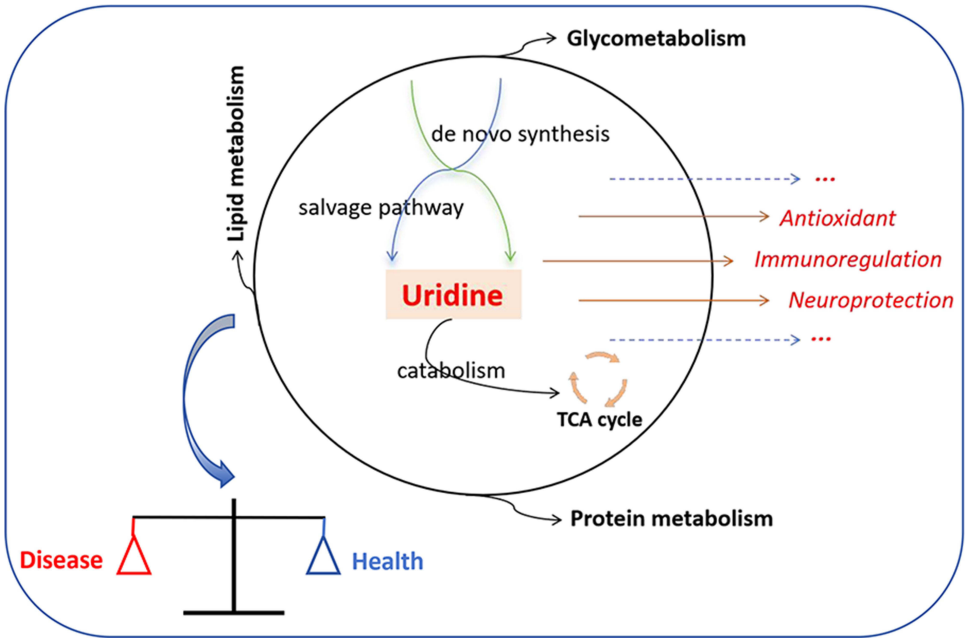
Abstract: Uridine plays a major role as a key biomolecule in health maintenance and disease treatment. Here, we comb and summarize a large amount of data on the important role of uridine in health, disease and treatment in the past 30 years, conduct a comprehensive and in-depth discussion, and give unique insights and overview on the current situation and difficulties of the application of uridine in disease treatment. The review aims to provide new perspectives and implications for uridine research and to promote further application of uridine in the medical field.

Keywords: uridine, uridine homeostasis, uridine catabolism

Graphical Abstract



Introduction

Uridine is a pyrimidine nucleoside composed of uracil and ribose, which can be used not only to synthesize genetic material such as RNA and DNA, but also to provide a material basis for various metabolic processes.[1] In the human

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body, uridine is present in the blood and cerebrospinal fluid. Since most tissues are unable to synthesize uridine independently, they rely on the circulatory system to uptake exogenous uridine to maintain basal cellular functions. Therefore, blood uridine homeostasis has a great impact on systemic metabolism, and the appropriate uridine level is crucial for health maintenance, while the abnormal uridine concentration can lead to the occurrence and development of various diseases.[2] Uridine, as an endogenous metabolite, is considered safe. For the aforementioned reasons, uridine is also widely used in clinical settings. Uridine, as an important biomolecule, holds great potential in maintaining health and treating diseases. Here, we focus on the vital role of uridine in health, disease, and therapy, as well as the innovative advancements in related research, with the aim of providing insights into the current state of research and future perspectives on relevant topics.

The Synthesis and Catabolism of Uridine

De novo synthesis, salvage synthesis, and catabolism are the three metabolic pathways of pyrimidine nucleotide metabolism. Uridine is part of the pyrimidine nucleotide family and can be synthesized intracellularly through de novo synthesis. The de novo synthesis of uridine originates from glutamine and aspartate, with the first step catalyzed by CAD. CAD is a multi-domain enzyme composed of carbamoyl-phosphate synthase 2 (CPSII), aspartate transcarbamoylase (ATC) and dihydroorotase (DHO). In the de novo synthesis pathway, CAD catalyzes glutamine and aspartate to produce intermediate metabolites, namely carbamoyl phosphate, aspartyl carbamoyl phosphate, and dihydroorotate. This process leads to the formation of the pyrimidine ring. Subsequently, under the catalysis of dihydroorotate dehydrogenase (DHODH), dihydroorotate is converted into the important intermediate, orotate. Then, orotate phosphoribosyltransferase and orotidine 5'-phosphate decarboxylase sequentially transform orotate into orotidine monophosphate (OMP) and uridine monophosphate (UMP). UMP is dephosphorylated by a nucleotidase to uridine (Figure 1A).

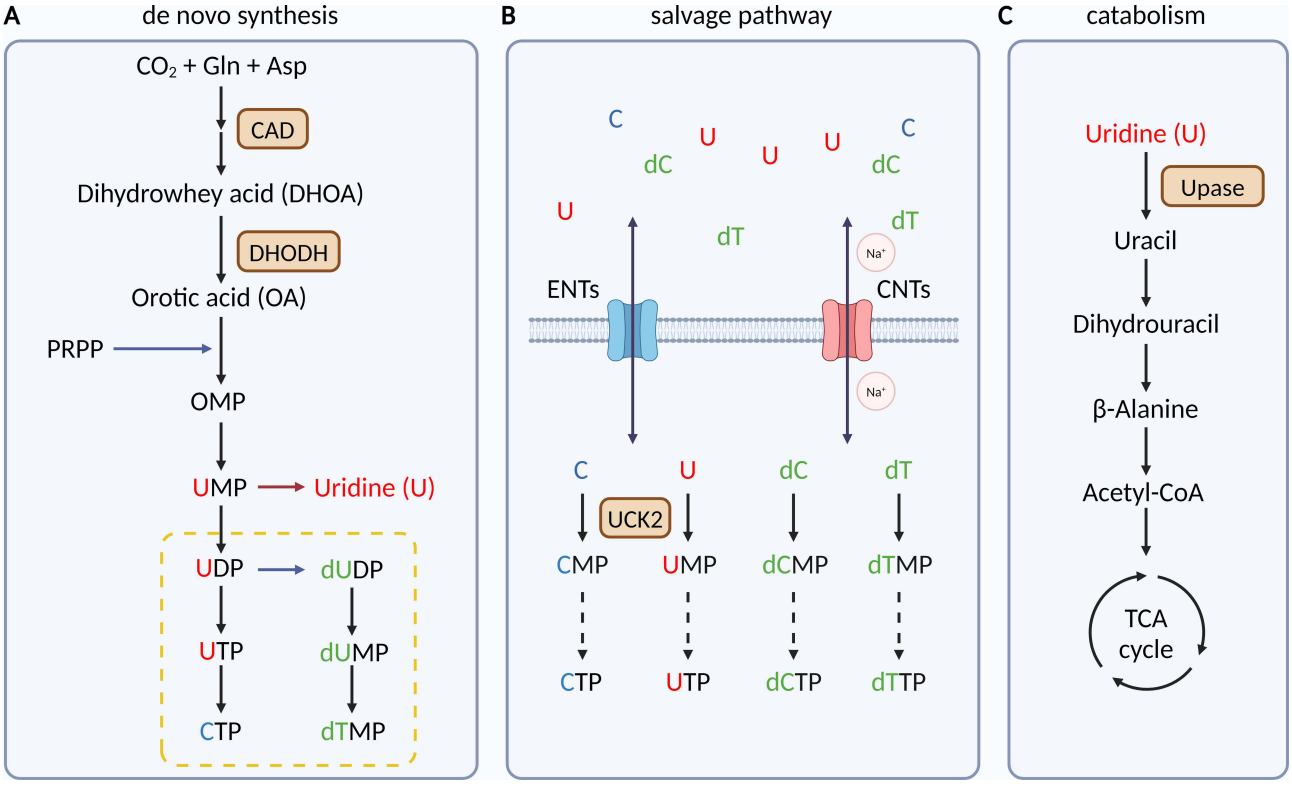

Figure 1 The synthesis and catabolism of uridine. (**A**) De novo synthesis; (**B**) salvage pathway, ENTs: the SLC29 family balanced nucleoside transporters; CNTs: the SLC28 family concentrated nucleoside transporters; (**C**) catabolism.
Abbreviation: TCA, tricarboxylic acid.

In addition to the de novo synthesis pathway, the pyrimidine salvage synthesis pathway is also an important way to obtain uridine. This pathway utilizes free pyrimidine bases or pyrimidine nucleosides and converts them into uridine nucleotides through fewer steps.This pathway is particularly important in certain tissues, such as the brain and bone marrow, which may lack the capacity of the de novo synthetic pathway. Uridine can be obtained directly from the decomposition of UTP, CTP, and this process is reversible. When the endogenous synthesis supply is insufficient, uridine is mainly used through exogenous ingestion to maintain its homeostasis to ensure normal cell growth and function. The SLC28 family concentrated nucleoside transporter (CNT) and the SLC29 family balanced nucleoside transporter (ENT) are two types of nucleoside transport family proteins currently known.[3] The CNT family includes three transporters: hCNT1, hCNT2, and hCNT3 (corresponding to SLC28A1, SLC28A2, and SLC28A3, respectively). These transporters are sodium ion-dependent, and they use an electrochemical gradient of sodium ions across the membrane to drive nucleoside transport. The ENT family consists of four transporters: hENT1, hENT2, hENT3, and hENT4 (corresponding to SLC29A1, SLC29A2, SLC29A3, and SLC29A4, respectively). These transporters are of the sodium-independent type and they undergo energy-independent nucleoside transport independent of the sodium gradient. CNT and ENT are two important families of nucleoside transporters that play key roles in nucleoside transport both inside and outside of the cell.[4,5] In the salvage synthesis pathway, uridine-cytidine kinase 2 (UCK2) plays a key role in phosphorylation pyrimidine nucleosides (uridine and cytidine) into the corresponding nucleoside monophosphates (UMP and CMP) for the subsequent generation of UDP/UTP, CDP/CTP, etc (Figure 1B).

Notably, the maintenance of uridine homeostasis also requires the proper catabolic involvement of uridine. During uridine catabolism, uridine phosphorylase (UPase) plays a leading role.[6] There are two homologous forms of UPase in vertebrates, namely UPase1 (encoded by the UPP1 gene) and UPase2 (encoded by the UPP2 gene). Among both enzymes, UPase1 appears to play a more important role in maintaining uridine homeostasis, being ubiquitously expressed, and knockout of the UPP1 gene or weakening of UPase1 enzyme activity increases uridine levels in plasma and tissues. The UPase2 is considered as a liver-specific protein, and the UPase2 enzyme activity can also significantly affect the level of endogenous uridine in the liver, which is also indispensable for the pyrimidine salvage pathway. Uridine can be degraded by UPase to uracil, while the latter can be further decomposed into dihydrouracil and N-carbamyl-β-alanine by dihydropyrimidine dehydrogenase and dihydropyrimidine enzyme, and then converted to β-alanine and acetyl-CoA by β-urea alanase (Figure 1C). β-Alanine can enter other tissues or be excreted, while acetyl-Coenzyme A can increase the acetylation level of intracellular proteins, so uridine can mediate cellular pathophysiological processes at the post-translational modification level of proteins.

The Role of Uridine in Health Maintenance

Antioxidant Properties of Uridine

Uridine is a nucleoside in an RNA structure that consists of a uracil base and a ribose. It not only plays an important role in nucleic acid synthesis, but also shows a potential importance in maintaining the cellular redox balance and antioxidant protection. Uridine has been reported to induce changes in the ratios of NAD/NADH and NADP/NADPH. These are essential coenzymes for cellular metabolism, redox and antioxidant processes, and are key factors in maintaining the cellular redox state.[7,8] In addition, uridine also regulates antioxidant enzyme activity and mitochondrial function to maintain its antioxidant properties. Uridine was found to enhance the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPX), thus enhancing cellular defense against ROS.[9–11] Mitochondria are the main ROS producing sites in cells, and uridine is thought to regulate the mitochondrial respiratory chain through DHODH to normalize mitochondrial structure and function. Additionally, the uridine derivative UDP, acting as an activator of the mitochondrial ATP-dependent potassium channel (mitoK_{ATP}), can activate potassium cycling in mitochondria, resulting in mild uncoupling of mitochondria and inhibition of ROS production.[10,12–14] Uridine is also able to affect multiple signal transduction pathways including NF- κB and MAPKs, Nrf 2, which are closely involved in the cellular response to oxidative stress. By regulating these pathways, uridine helps to maintain the antioxidant state within the cells.[11,15–17] Moreover, although uridine is relatively weak in its direct free radical scavenging ability, it can indirectly participate in ROS clearance through conversion to other antioxidant molecules.[18]

The Role of Uridine in Immune Regulation

Uridine has an important role in immune regulation. Uridine is involved in the regulation of immune signaling pathways, which can affect the production and release of inflammatory cytokines, such as TNF-α and IL-1β, thereby alleviating the inflammatory response and hyperactivation of the immune system.[17] Increasing evidence suggests that uridine is critical for maintaining cellular function and energy metabolism.[7] Uridine also has a regulatory effect on the energy metabolism of immune cells, which is crucial for maintaining the metabolic activity of immune cells and enhancing their energy supply and functional performance.[19]

Uridine can modulate the function of the immune system and enhance the body's immunity,[20] which may be related to the important role of uridine in maintaining the normalization of mitochondrial structure and function. Mitochondria occupy a critical position in immunobiology, not only in terms of bioenergetic function, but also in the metabolism and signaling of immune cells.[21] Mitochondria are regarded as the main metabolic regulators of T cells because they can regulate different stages of the adaptive response of T cells.[22] The immune system, and especially the T cells, requires a functional mitochondrial respiratory chain.[23] Uridine is thought to regulate the mitochondrial respiratory chain through DHODH to normalize the mitochondrial structure and function. The study by Battaglia S et al[24] found that uridine supplementation protected the proliferative ability of T cells from mitochondrial toxic antibiotics.

In addition to the classical role of genetic material synthesis, uridine can also be converted into a variety of other bioactive molecules to play multitarget roles. A number of studies have shown that extracellular nucleotides (ATP, UDP, etc.) can act as immunomodulatory mediators during inflammatory responses by binding to P2 purinergic receptors (such as P2Y6), which can be released by damaged cells to activate the immune response under inflammatory conditions.[25–27] Several studies[28,29] also demonstrated that uridine abolished mitochondrial toxicity caused by antiretroviral therapy in HIV infected patients. These findings undoubtedly suggest a close association between uridine and immunity.

Neuroprotective Effects of Uridine

The protective effect of uridine on the nervous system is multifaceted. First, the anti-inflammatory and antioxidant properties of uridine can protect a variety of cells, including nerve cells, from inflammation and oxidative damage.[30] Secondly, uridine is the precursor of CDP-choline synthesis.[31] In the nervous system, CDP-choline is not only involved in the construction and maintenance of cell membranes, but is also associated with the synthesis of neurotransmitters.[32,33] For example, choline is the precursor for the synthesis of acetylcholine (ACh), which is a key neurotransmitter in the central and peripheral nervous systems, involving various cognitive functions such as learning, memory, and attention. Moreover, CDP-choline may also have effects on neurodegenerative diseases and repair processes after nerve injury by affecting biological lipid metabolism and cell signaling in nerve cells.[34–36] CDP-choline, in animal models of demyelinating diseases, such as multiple sclerosis, shows the potential to promote remyelination and nerve repair.[37]

In addition, a study[38] noted that uridine protects cortical neurons from death caused by glucose deprivation, which may involve the role of uridine phosphorylase. This suggests that uridine may exert neuroprotective effects through specific enzymatic action. Uridine was also able to mitigate morphine-induced conditioned place preference and to modulate glutamate/γ-aminobutyric acid levels in the mouse prefrontal cortex.[39] Uridine can also have antiepileptic effects on seizures by regulating dopamine release and receptor expression.[40,41] Alternatively, the neuroprotective effects of uridine is reflected in the role of uridine in energy metabolism and cellular repair processes. It enhances energy supply by enhancing mitochondrial function and protects neurons from metabolic stress.[15] The neuroprotective effect of uridine was also correlated with reduced apoptosis.[30,42] Overall, the neuroprotective effect of uridine is a multi-faceted, multi-level process involving multiple links, including antioxidant defense, immune regulation, energy metabolism and cellular repair, and anti-apoptosis. The role of uridine in health maintenance were shown in Figure 2.

The Crosstalk Between Uridine and Substance Metabolism

Uridine can play a role in various biosynthetic processes by being converted into other bioactive molecules, thus possessing multiple biological functions.[18] On the one hand, uridine can participate in protein glycosylation through the formation of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc).[43] On the other hand, uridine can also

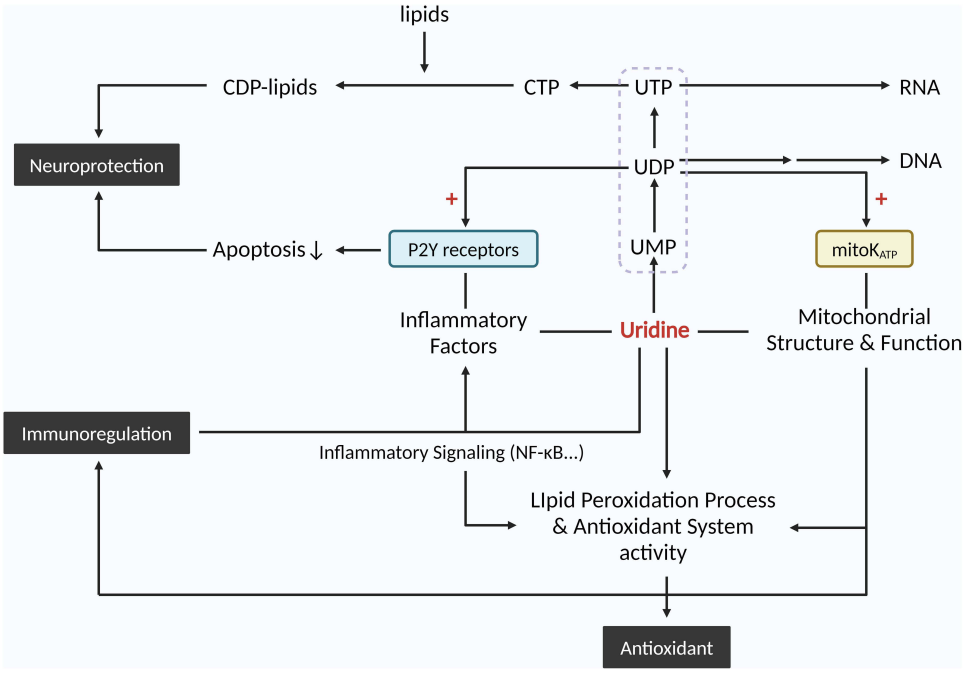

Figure 2 The role of uridine in health maintenance.

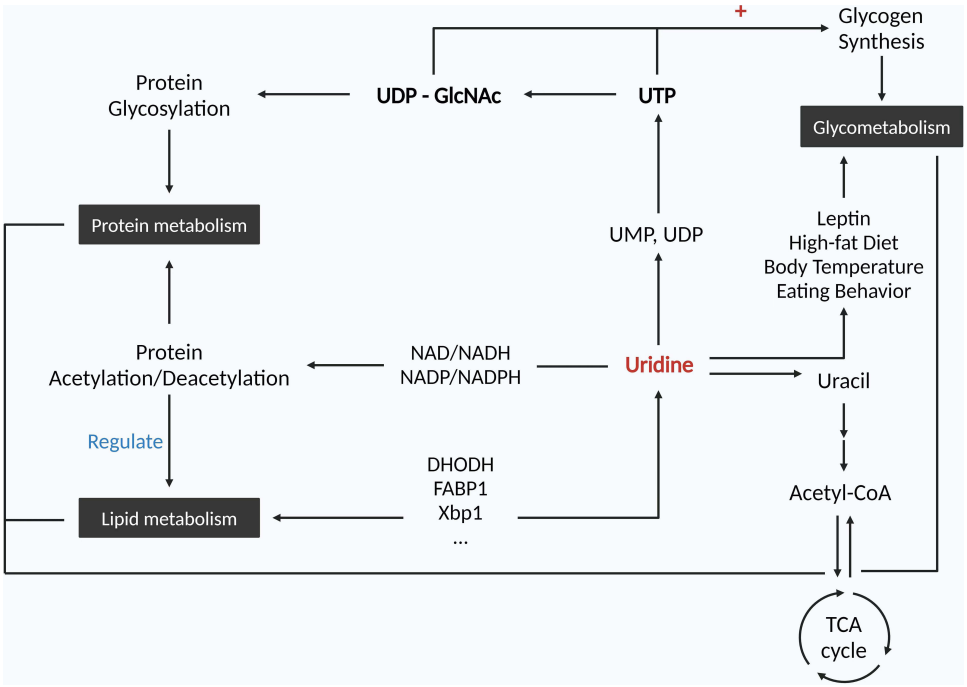

Figure 3 The crosstalk between uridine and substance metabolism.

promote the biosynthesis of cell membrane phospholipids by converting it to cytidine triphosphate (CTP).[44] In addition, uridine also regulates biological rhythm, including body temperature rhythm and circadian rhythm.[45] As an important intermediate material in the biological network of the body, uridine is mutually interactive and complex (Figure 3).

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Uridine and Protein Metabolism

O-acetylglucosamine (O-GlcNAc) can modify proteins in various metabolic pathways. Uridine can be converted into UDP-GlcNAc (a protein O-GlcNAc substrate), which is then attached to the hydroxyl group on the serine or threonine residues of the protein chain to form the O-GlcNAc modification.[46,47] This is a highly dynamic and ubiquitous mode of protein modification that is rapidly emerging as a key regulator of key biological processes. The role of uridine in O-GlcNAc modification is closely related to protein phosphorylation.[48] The interaction between these two modifications can affect protein function and lead to the occurrence and development of related diseases.

In addition to UDP-GlcNAc, the synthetic product of uridine, its degradation product acetyl-coenzyme A also plays an important role in protein metabolism.[7] In addition to the synthesis and degradation products that can link to protein metabolism, uridine itself can also induce the changes in NAD/NADH and NADP/NADPH ratios.[7,8] This may activate the NAD-regulated deacetylases, leading to increased protein deacetylation. It should also be noted that the catabolic amino acids of proteins can also provide a carbon or nitrogen source for uridine synthesis, and influence uridine concentration through different metabolic pathways.

Uridine and Lipid Metabolism

The relationship between uridine as a pyrimidine metabolism intermediate and lipid metabolism is also widely confirmed. DHODH is a mitochondrial membrane-bound respiratory chain coupling enzyme that plays an important role in the process of pyrimidine metabolism.[49] Weakening of the DHODH enzymatic activity can cause microvesicular fat deformation, and this condition can be relieved after uridine supplementation.[50] Notably, uridine did not have any effect on DHODH enzyme activity, which most likely reversed lactate-induced intracellular lipid accumulation in a way other than regulating DHODH enzyme activity.[7]

Uridine and fat are closely related, and both are metabolized through the hepatic-biliary pathway. Uridine is synthesized in adipose tissue during fasting and its levels affect the stability of blood lipids. Short-term uridine supplementation prevents drug-induced hepatic fat accumulation, while long-term exogenous uridine supplementation causes fatty liver disease.[2] It has been reported that long-term uridine supply suppresses the expression of liver-specific fatty acid binding protein 1 (FABP1), which may be an important cause of fatty liver, namely, long-term uridine supply may be a driver of fatty liver.[51] Additionally, the X box-binding protein 1 (Xbp1) plays a role in uridine metabolism and is activated in response to ER stress in adipose tissue. Its overexpression can increase uridine synthesis and inhibit fat accumulation.[52,53] Another example of uridine levels affecting lipid stability is that inhibition of UPase2 suppresses hepatic lipid accumulation caused by drugs by increasing the concentration of endogenous hepatic uridine.[2]

In addition, it has been shown that uridine can alter the ratio of NAD^+/NADH and $NADP^+$ / NADPH in the liver, and regulate the protein acetylation profile to regulate lipid metabolism.[7] In conclusion, uridine is closely related to lipid metabolism, and the specific mechanism is complex and still needs further study.

Uridine and Glucose Metabolism

Uridine as a UTP and UDP-glucose precursor can activate glycogen synthesis.[15,54] Leptin is a protein hormone secreted by adipose tissue. Its main function is to regulate energy balance, inhibit appetite, and reduce fat storage in adipocytes. Uridine has been reported to influence glucose metabolism through leptin. Namely, uridine supplementation improved glucose tolerance in mice on a high-fat diet. While in the absence of leptin, uridine supplementation worsened glucose tolerance.[1] Uridine has also been reported to affect insulin signaling and glucose tolerance profiles.[31] Furthermore, prolonged uridine supplementation leads to elevated blood glucose levels and insulin resistance. However, under high-fat diet conditions, uridine supplementation reduces blood glucose levels. This suggests that the regulation of glucose metabolism by uridine is influenced by the calorie levels in the diet.[55] The increased leptin levels associated with a high-fat diet may contribute to the dual effects of uridine on glucose tolerance. In addition, it has been shown that high-dose uridine supplementation may reduce rodent body temperature,[56] and uridine is likely a driving force of thermoregulation during fasting and refeeding,[1] which is undoubtedly another strong evidence of the association of uridine and glucose metabolism.

The Role of Uridine in the Disease

The continuous and stable circulating uridine level is the basis of the normal operation of various biological processes of the body, and the destruction of uridine homeostasis is bound to affect this, and then lead to disease.[57] The association of uridines with the disease is presented in Table 1.

Metabolic Diseases

Fatty Liver Disease and Diabetes Mellitus

The liver is the organ most affected by ectopic lipid accumulation.[58] Disruption of uridine homeostasis is closely associated with the accumulation of hepatic lipids.[7] Exogenous uridine supplementation inhibited hepatic steatosis induced by several drugs, such as tacacitabine, fenofibrate, and tamoxifen.[2,31] Alternatively, in a mouse model, uridine supplementation alleviated high-fat diet-induced obesity and non-alcoholic fatty liver disease by regulating the gut microbiota.[59]

The development of diabetes is closely associated with decreased sensitivity to insulin signaling, and studies have shown that uridine can increase insulin sensitivity by inhibiting inflammatory responses and oxidative stress.[60] At the same time, uridine reduced blood glucose levels and improved glucose tolerance and diabetes-induced myocardial injury in diabetic mice. Mechanistically, uridine is protective against diabetes-mediated damage to cardiac mitochondrial function and structure, and against disruption of the mitochondrial quality control system in the diabetic heart.[61]

Diabetic vasculopathy is one of the main complications of diabetes. Its cause is that long-term hyperglycemia leads to abnormal expression of cytokines that maintain vascular homeostasis, resulting in adverse reactions such as inflammation and oxidative stress, causing vascular endothelial structural changes, and then dysfunction. According to the occurrence mechanism of vascular lesions, the effect of uridine on diabetic vascular complications is closely related to the endothelial cell disorders. Endothelial cell dysfunction is a pathophysiological feature leading to large and microvascular

Table 1 Urine in Disease

Diseases	Uridine-Related Pathogenesis or Roles
Hepatic adipose infiltration	Uridine disorder causes liver lipid accumulation and lipid metabolism disorder; Uridine modulates gut microbes to alleviate high-fat diet-induced obesity and non-alcoholic fatty liver disease.
Diabetes mellitus and its complications	Uridine can increase insulin sensitivity through inhibition of inflammatory response and oxidative stress; Uridine regulates protein O-GlcNAc modification by forming UDP-GlcNAc, and improves diabetes and its complications through CTP and mechanisms of glycogen synthesis.
Obesity	Overexpression of Xbp1 increases leptin and uridine synthesis and inhibited fat accumulation.
Acute lung injury in sepsis	Uridine inhibits oxidative stress, inflammatory response as well as ferroptosis to alleviate acute lung injury induced by LPS.
Osteoarthritis/Rheumatoid arthritis	Uridine improves arthritis by alleviating the aging of chondrocytes and mesenchymal stem cells.
Acute myocardial infarction and its complications	Uridine can improve myocardial ischemia and ischemia-reperfusion injury through energy homeostasis and action on mitoKATP channels.
Organ fibrosis	Uridine can improve fibrosis progression by inhibiting the inflammatory response process.
Alzheimer disease (AD)	Uridine exerts positive effects on synaptic membrane formation as well as synaptic function by synthetic CDP-choline.
Hypoxic-Ischemic Encephalopathy (HIE) / hyperoxide brain injury	Apoptosis and oxidative damage inhibition.
Tumors	The disruption of uridine homeostasis promotes DNA damage and tumor development; Aberrant expression of uridine metabolism genes may promote tumor progression.
Primary mitochondrial disease / Duchenne muscular dystrophy	Rescue or ameliorate the mitochondrial dysfunction.
Pyrimidine nucleotide carrier deficiency / congenital erythropoiesis anemia	Enhance the proliferative capacity of human hematopoietic stem cells and promote tissue regeneration and repair.

complications of diabetes.[55] Uridine participates in protein O-GlcNAc modification through the formation of UDP-GlcNAc. O-GlcNAcylation is involved in the regulation of various biological processes, including nuclear transport, translation, transcription, signal transduction, cytoskeletal reorganization, proteasomal degradation, and apoptosis.[62,63] While increased O-GlcNAc levels are thought to be a pathological contributor to glucose toxicity and insulin resistance, a major hallmark of diabetes and diabetes-related cardiovascular complications.[64,65]

Diabetic neuropathy is one of the common chronic complications of diabetes mellitus. It is due to the damage to the nervous system caused by prolonged hyperglycemia. This lesion can affect the nerves in many parts of the body, including the limbs, autonomic nerves and so on. Cytidine triphosphate (CTP), a derivative of uridine, promotes the resynthesis of phosphatidylinositol, an important neurocell membrane component. Thus uridine can restore nerve fiber function in diabetic patients through a mechanism of CTP synthesis. On the other hand, in the presence of glucose accumulation in the nerves of diabetic patients, exogenous uridine supplementation can reactivate the mechanism of glucose to glycogen to improve neurometabolism.

Obesity

Obesity is a metabolic disease caused by excessive fat accumulation. It has been shown that the rhythm of uridine after meals is disrupted in mice fed with a high-fat diet or that are obese, and uridine supplementation can relieve abnormal uridine levels in states of obesity or high-fat diets, thereby mitigating obesity.[1,66] Deng et al[1] found that the increase and maintenance of plasma uridine levels caused by fasting were critically dependent on adipocytes. A significant increase in uridine levels was observed in fat biopsies from HIV infected patients with lipodystrophy,[67] indicating that excessive production of uridine may contribute to the loss of adipose tissue. The elevation of plasma uridine in fasting depends on pyrimidine biosynthesis in adipocytes, which occurs concurrently with high levels of lipolysis.[52] However, it is unclear whether these two processes are mechanistically linked in adipocytes. The elevation of plasma uridine is essential for the decrease in body temperature during fasting. When fasting, adipocytes are responsible for synthesizing uridine. On one hand, when uridine synthesis increases, heat loss increases, body temperature drops, and fat mass decreases.[1] On the other hand, the activation of uridine synthesis in adipocytes during fasting is also a potential mechanism for triggering triacylglycerol mobilization, a process that can reduce fat mass.[68]

In addition to energy storage, adipose tissue secretes leptin, which is closely related to the occurrence and development of obesity. Xbp1 is a transcription factor involved in the ER stress response, and its overexpression increases leptin and uridine synthesis and suppresses fat accumulation.[52,69] While adiposolysis induces the expression of Xbp1 in adipocytes, which forms a circulatory mechanism that accelerates the loss of fat mass.[52] CAD, as the rate-limiting enzyme in uridine biosynthesis, was reported to be efficiently activated by Xbp1, suggesting that the loss of fat mass triggered by Xbp1 is dependent on pyrimidine biosynthesis.[52] These findings suggest that stimulation of the adipocyte uridine synthesis pathway may be a promising potential therapeutic target in obesity.

Acute Lung Injury in Sepsis

Sepsis is a systemic inflammatory response syndrome caused by an infection, which presents in the lungs as acute lung injury (ALI)/acute respiratory distress syndrome(ARDS).[70] In the lipopolysaccharide (LPS)-induced sepsis model, uridine supplementation can significantly reduce the systemic inflammatory response. This is thought to be related to inhibiting the expression of HSP72 and the activity of NF-KB pathway, thus inhibiting the overactivation of inflammatory factors.[15] Similarly, the investigators also found that exogenous uridine supplementation inhibited oxidative stress, inflammatory response as well as ferroptosis to alleviate acute lung injury induced by LPS.[71] In this model, the investigators found significant elevation of the uridine derivative UDP and increased expression of the P2Y6 in lung tissue, and knockdown of P2Y6 attenuated LPS-induced inflammatory response and acute lung injury.[72] As reported,[73] P2Y6 is over-expressed in acute lung injury-related immune cells (including macrophages, neutrophils and T cells), which helps to mediate pro-inflammatory responses. UDP binding to P2Y6 acts as an immunoregulatory mediator during the inflammatory response, triggering the release of cytokines and chemokines, thereby promoting the recruitment of immune cells to sites of inflammation or infection.[74–76] And the disruption of lung homeostasis by inflammatory cell infiltration is considered a key factor in the progression of ALI / ARDS.[77] However, it is noteworthy that the P2Y6

receptor was also reported to exert inhibitory leukotriene-dependent type 2 allergic pulmonary inflammatory response effects in alveolar macrophages.[78] Together, these studies suggest that uridine can inhibit acute inflammatory response and lung injury through multiple routes, and can also be converted into other metabolites such as UDP to exert corresponding cell-determined anti-inflammatory or pro-inflammatory effects.

Osteoarthritis and Rheumatoid Arthritis

Osteoarthritis is a joint degenerative disease with an extremely high incidence in the elderly, and inflammation plays an important role in the manifestation of clinical events in osteoarthritis.[79] Specifically, certain cytokines exhibit proinflammatory properties that are clearly activated during the course of the disease and significantly alter the homeostasis of the joint environment.[80] A previous study reported[9] that uridine improved osteoarthritis by reducing the aging of chondrocytes and mesenchymal stem cells. Another study[81] showed that the expression of UPP1 was increased during the development of osteoarthritis. The level of IL-1β in the articular effusion of osteoarthritis patients was inversely correlated with the uridine concentration, and exogenous uridine supplementation significantly alleviated the damage of cartilage and inflammation in the synovium, and promoted the homeostasis of cartilage, suggesting that the UPP1/uridine axis is involved in the development and development of osteoarthritis. In addition, it was reported that UDP is highly expressed in rheumatoid arthritis and promotes its progression by increasing IL-6 production by promoting P2Y6 activity.[82] These studies suggest that uridine can inhibit the development of osteoarthritis / rheumatoid arthritis by inhibiting inflammatory responses.

Acute Myocardial Infarction and Its Related Complications

Acute myocardial infarction (AMI) is a process of acute myocardial necrosis caused by persistent and severe myocardial ischemia. Myocardial ischemia-reperfusion injury is involved in the pathological processes of myocardial infarction and post-infarction myocardial remodeling. Inflammatory response of acute myocardial infarction plays a key role in determining the area size of myocardial infarction, and a sustained pro-inflammatory reaction can lead to adverse ventricular remodeling after myocardial infarction, making inflammation an important therapeutic target to improve the prognosis of AMI.[83]

A previous study[84] examined the effects of uridine and its nucleotide derivatives (UMP, UDP, UTP) on the cardiac contractility of the left ventricle in isolated perfused rat hearts subjected to one hour of regional ischemia. It was found that uridine and its derivative UMP could prevent the inhibition of the contractile function of the ischemic myocardium in the isolated heart. Meanwhile, uridine and UMP were also reported to prevent myocardial shock during ischemic reperfusion in the isolated rat heart.[85] Additionally, Irina B. Krylova et al[10] showed that the administration of uridine to mice five minutes prior to the ligation of the left coronary artery completely prevented the increase in lipid peroxide production and the decline in GSH levels and SOD activity. This suggests that uridine alleviates the oxidative metabolic disorder in the ischemic myocardium and restores the balance between the lipid peroxidation process and the activity of the antioxidant system, which is important for maintaining intracellular redox homeostasis during ischemia. The study also found faster clearance of intravenous uridine from the blood in acute ischemic animals compared with normal animals, suggesting that uridine is involved in the activation of intracellular anti-ischemic defense mechanisms.[10] In fact, the cardioprotective effect of uridine is associated with the activation of the mitochondrial ATP-dependent K^+ (mitoK_{ATP}) channels. UDP is a potent metabolic activator of the mitoK_{ATP} channels,[86] uridine administration significantly increased UDP content, thereby activating mitoK_{ATP} channels. It should be noted that UDP is unstable and unable to penetrate the cell membrane, and the supply of exogenous uridine is required for UDP and UTP synthesis in the ischemic myocardium. Notably, the protective effect of uridine on lipid peroxidation and antioxidant activity could be attenuated by the concurrent use of 5-HD (mitoK_{ATP} channel inhibitor). These results suggest that mitoK_{ATP} channels are involved in the myocardial protective effects of uridine. In summary, the aforementioned studies demonstrate that uridine can ameliorate myocardial ischemia and ischemia-reperfusion injury through the maintenance of energy homeostasis and by acting on the mitoK_{ATP} channels.

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Organ Fibrosis

Organ fibrosis is a pathological process of stromal hyperplasia caused by chronic inflammation. In a carbon tetrachloride-induced liver fibrosis model, uridine alleviated the level of hepatic inflammation and suppressed the expression of hepatic fibrosis markers by inhibiting NF-KB activation. Moreover, uridine also alleviates carbon tetrachloride-induced liver toxicity by inhibiting oxidative stress-induced apoptosis in hepatocytes.[87] In addition, CPBMF65 (a UPP1 inhibitor) was reported to increase the levels of endogenous uridine and inhibit the progression of carbon tetrachloride-induced liver fibrosis in mice.[88]

Pulmonary fibrosis is a chronic and progressive lung disease. A previous study[89] has indicated that in a bleomycin-induced pulmonary fibrosis mouse model, uridine can alleviate pulmonary inflammation, as evidenced by a reduction in white blood cells and pro-inflammatory cytokines in the bronchoalveolar lavage fluid. Additionally, exogenous supplementation of uridine can decrease collagen deposition in the lung interstitium. In cellular models, uridine can inhibit the expression of collagen and TGF-β in primary lung fibroblasts, suppress the release of pro-inflammatory cytokines from human lung epithelial cells, and reduce the production of reactive oxygen species in human neutrophils. Overall, uridine can improve the progression of fibrosis by inhibiting the inflammatory response process.

Nervous System Diseases

Alzheimer's Disease

Alzheimer's disease (AD), a neurodegenerative disease with progressive cognitive dysfunction, is the leading cause of cognitive impairment in the elderly population.[90] Recent studies[91–93] have noted lower uridine levels in the blood of patients with AD dementia, suggesting that uridine may be associated with clinical progression in AD. This low level may be related to lower nutrient intake in AD or increased demand for uridine in the regenerative synaptic membrane.[93,94] Uridine is a precursor for the synthesis of CDP-choline, which is a key intermediate in the production of cell membrane phospholipids, particularly playing an indispensable role in the synthesis of phosphatidylcholine (lecithin). Phosphatidylcholine is one of the main components of the cell membrane, essential for maintaining the integrity and function of the cell membrane, and is required for the formation of neuronal cell membranes. Uridine supplementation was reported to have positive effects on synaptic membrane formation and synaptic function,[93,95,96] which may alleviate synaptic dysfunction in AD.

Hypoxic-Ischemic Encephalopathy (HIE) and Hyperoxide Brain Injury

Hypoxic-Ischemic Encephalopathy (HIE) in neonates refers to a clinical syndrome characterized by ischemia and hypoxia of brain tissue due to insufficient blood flow and/or oxygen supply during the perinatal period, resulting in brain dysfunction or injury. This condition is one of the severe neurological disorders in the neonatal period and may lead to long-term neurological sequelae, including cognitive impairments, epilepsy, cerebral palsy, and others. Several studies have reported on the neuroprotective manipulation of uridine in HIE. For example, Cansev M et al found that uridine dose-dependently reduced brain damage in a neonatal HIE rat model by reducing apoptosis.[97] Goren B et al also observed that exogenous uridine supplementation may improve the cognitive effects of rats with brain injury by reducing apoptotic cell death in the early neonatal period.[98] In addition, uridine could also provide neuroprotection in a neonatal rat model of HIE by reducing apoptosis and inhibiting histone deacetylase (HDAC) activity.[99] It is evident from these research findings that the neuroprotective role of uridine in HIE is associated with the reduction of apoptosis. It was reported[30] that uridine nucleotides (UTP and UDP) can stimulate P2Y receptors (P2Y2, P2Y4, and P2Y6) to provide neuroprotection by reducing apoptosis. In the hyperoxic brain injury model, uridine was also observed to provide benefits to neonatal brain injury and long-term cognitive deficits through inhibition of apoptosis[100] and oxidative damage.[101]

Sciatic Nerve Injury

Sciatic nerve injury refers to damage to the longest nerve in the body, the sciatic nerve, which can be caused by compression, traction, laceration, or other forms of injury. Based on current data, the protective effect of uridine in sciatic nerve injury is primarily associated with its conversion to CDP-choline and its anti-apoptotic and antioxidant properties.

Uridine administration can elevate levels of CDP-choline in the brains of rodents.[102] Several previous studies[34,35,103] have indicated that CDP-choline can improve neural regeneration and functional recovery in models of sciatic nerve injury. Uridine may also provide benefits for sciatic nerve injury through its anti-apoptotic and antioxidant properties,[42] as well as by enhancing neural adhesion and increasing the number of myelinated axons.[104]

Tumors

The presence of uridine in the tumor microenvironment is important for the metabolism and survival of cancer cells. Uridine and its derivatives play a role in various biological processes in tumor cells, including nucleic acid synthesis, energy metabolism, and signaling.[105] In a range of mammals, including humans, plasma uridine concentrations are tightly controlled in the appropriate range.[45,106] However, disruption of this rigid homeostasis has pathophysiological consequences. A previous study[107] has reported that disruption of uridine homeostasis promotes DNA damage and tumorigenesis, demonstrating the crucial regulatory role that uridine and its derivatives play in tumorigenesis and development.

Under glucose-limited conditions, cancer cells can utilize uridine as an alternative source of nutrients and energy. Uridine phosphorylase 1 (UPP1) plays a crucial role in this process by releasing uridine-derived ribose, which promotes central carbon metabolism as well as supports redox homeostasis, survival, and proliferation of cancer cells.[108]

Concentrations of uridine are high in the tumor microenvironment. Cancer cells adapt to nutrient deficiencies by sensing the concentrations of glucose and uridine in their environment. Uridine utilization is also considered to be an important compensatory metabolic process in cancer cells under conditions of nutrient deprivation.[108,109] In addition, it has been reported[110] that uridine diphosphate glucose (UDP-Glc), a uridine derivative, plays an inhibitory role in lung cancer metastasis. UDP-Glc interacts with the RNA-binding protein HuR and competitively inhibits the stabilizing effect of HuR on SNAI1 mRNA, thereby inhibiting lung cancer metastasis. This ambiguous relationship between uridine and tumors is also associated with key enzymes involved in uridine metabolism. UCK2 is the rate-limiting enzyme in the pyrimidine nucleotide salvage pathway, and its overexpression has been found to promote malignant phenotypes in various tumors.[111,112] In addition, down-regulation of UCK2 can alter the tumor microenvironment. Inducing cell cycle arrest and activating a secretory phenotype associated with senescence may improve the tumor immune microenvironment and enhance the sensitivity of tumor cells to T-cell-mediated killing.[113] UPP1 plays an integral role in pyrimidine salvage and uridine homeostasis, and it is upregulated in various cancers including lung adenocarcinoma. UPP1 drives glycolytic metabolism both in vitro and in vivo, and it significantly modulates tumor sensitivity to glycolytic inhibitors.[114] In lung adenocarcinoma, UPP1 also enhances PD-L1 expression through the PI3K/AKT/mTOR pathway, inducing an immunosuppressive microenvironment that promotes tumor progression.[115] These findings suggest that targeting the uridine metabolic pathway may contribute to the treatment of cancer as well as metabolic disorders, and also the regulation of immune responses.

In summary, uridine and its metabolic pathways play vital roles in tumor metabolism, metastasis, immune microenvironment regulation, and as therapeutic targets. These findings provide new perspectives and potential strategies for cancer diagnosis, treatment and drug development.

Other Diseases

Caused by mitochondrial dysfunction, Primary Mitochondrial Diseases (PMDs) are a group of inherited metabolic disorders that are highly heterogeneous and can involve multiple systems and organs of the body, especially those tissues with high energy demands, such as the heart, muscles, and brain. These disorders may manifest as muscle weakness, cardiomyopathy, epilepsy, retinopathy, hearing loss, neurodegenerative symptoms, etc.[116,117] Currently, uridine supplementation can rescue impaired oxidative phosphorylation in PMDs.[118]

In addition, the beneficial effects of uridine have been demonstrated in skeletal muscle diseases. Duchenne Muscular Dystrophy is caused by the loss of functional dystrophin proteins secondary to a systemic metabolic disorder in skeletal muscle and cardiac myocytes. Uridine slowed the development of destructive processes in skeletal muscle and partially rescued mitochondrial dysfunction in skeletal muscle in Duchenne Muscular Dystrophy.[119] Also, uridine has been

reported to be used in the treatment of patients with pyrimidine nucleotide carrier defects[120] and congenital dyserythropoietic anemia,[121] which may be related to the fact that uridine enhances the proliferative capacity of human hematopoietic stem cells and promotes tissue regeneration and repair.

Uridine has been used as a therapeutic drug for orotic aciduria, a hereditary disorder characterized by excessive excretion of orotic acid in the urine.[122] Besides, uridine has also been reported to be used for the amelioration of colitis and arthritis.[123,124]

Exploration and Application of Uridine in Therapy

Having important physiological and pharmacological effects on multiple systems throughout the body, uridine has great potential as a candidate target for drug development. Several studies[28,29] have demonstrated that uridine eliminates mitochondrial toxicity induced by antiretroviral therapy in HIV-infected patients. Uridine analogs can have potent antiviral activity against HIV, hepatitis B and C, and herpesviruses by inhibiting key steps in the viral replication pathway.[125,126] The importance of uridine and its derivatives as targets in drug discovery is also reflected in the structural modification and drug design of uridine. Via chemical modification of its structure, the pharmacological and pharmacokinetic properties of uridine can be improved, including enhanced bioactivity, selectivity, metabolic stability, and absorption, as well as reduced toxicity.[127] 4-thiouridine (4SU), a uridine analog, differs from uridine by the substitution of a thiol group. It shows potent anti-inflammatory properties and has been reported to prevent experimental colitis and arthritis.[128] In addition, uridine derivatives such as 5-fluorouracil (5-FU)[129] and uramustine[127] are early-developed compounds with pharmacological activity, which have been shown to have significant antimetabolic effects in tumor therapy due to their ability to inhibit tumor cell proliferation by interfering with nucleic acid metabolism and DNA synthesis.

Uridine and its derivatives can directly act on cell surface P2Y receptors, such as P2Y2, P2Y4, and P2Y6, which are G-protein-coupled receptors. When activated, they can participate in the corresponding pathophysiological processes by initiating downstream pathways.[130] Therefore, the specific pyrimidine receptors that can be targeted by uridine and its derivatives are undoubtedly significant reference targets in drug development. In addition, human condensed nucleoside transporter protein 3 (hCNT3) is a transmembrane protein that transports uridine. By studying the molecular recognition and release mechanism between hCNT3 and uridine, uridine derivatives with high inhibitory activity can be designed.[131]

Therapeutic strategies for uridine are innovative. First, uridine can be delivered via multiple pathways, such as oral, injection, or topical application, which provides more options for disease treatment. Second, uridine-based mRNA modification technology also provides important support for the clinical application of uridine. In 2005, a study[132] by Katalin Karikó et al found that replacing uridine by introducing pseudouridine into mRNA can indeed reduce the immunogenicity of mRNA, thus solving a key challenge in the clinical application of mRNA technology. This technological breakthrough provides important technical support for the subsequent development of mRNA vaccines. A study[133] demonstrated that mRNA vaccines containing unmodified uridine induced potent type I interferon-dependent anti-tumor immunity in a melanoma model, suggesting that uridine has a great potential for mRNA vaccine development.

Additionally, uridine can serve as a source of nutrients and energy for cells under glucose-limited conditions, especially in pancreatic cancer cells.[108] This suggests that blocking the utilization of uridine by drugs in specific environments may lead to new options for cancer therapy. These innovative therapeutic strategies, which may improve therapeutic efficacy while reducing side effects, provide new directions for future drug development and disease treatment.

Summary and Prospects

As an endogenous metabolite, uridine not only provides the material basis for the synthesis and modification of intracellular macromolecular organic matter as well as the overall metabolic function of the organism, but also regulates various pathophysiological processes through multiple ways. Therefore, a stable uridine supply is crucial for maintaining cellular function and organismal homeostasis.[1] Currently, uridine and its derivatives are employed in treating various diseases, but some challenges and limitations persist, including resistance and side effect problems in tumors. In addition, further attention is needed on the optimal dosage and cycle of uridine use in treating various diseases.

Since uridine is crucial in health, disease, and therapy, further exploration of uridine-based drug development and therapeutic programs is essential moving forward. On the one hand, the structure of uridine can be modified and altered appropriately to develop more efficient and less toxic derivatives. On the other hand, trying to combine other therapeutic means, such as immunotherapy and targeted therapy, may improve the anti-tumor effect of uridine. Meanwhile, through an intensive investigation of uridine's mechanism of action, we can enhance our understanding of its role and potential risks in disease treatment. This will give clinicians precise dosing guidance and support personalized treatment.

Overall, uridine is a bioactive molecule with potential for various applications, playing a crucial role in maintaining health and treating diseases. A deeper understanding of uridine's biological functions, disease associations, and novel therapeutic approaches will hopefully result in significant advancements in the prevention and treatment of human diseases.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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 report no conflicts of interest in this work.

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