Trends in
Endocrinology & Metabolism

CellPress
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Opinion

Nucleosides are overlooked fuels in central carbon metabolism

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From our daily nutrition and synthesis within cells, nucleosides enter the bloodstream and circulate throughout the body and tissues. Nucleosides and nucleotides are classically viewed as precursors of nucleic acids, but recently they have emerged as a novel energy source for central carbon metabolism. Through catabolism by nucleoside phosphorylases, the ribose sugar group is released and can provide substrates for lower steps in glycolysis. In environments with limited glucose, such as at sites of infection or in the tumor microenvironment (TME), cells can use, and may even require, this alternative energy source. Here, we discuss the implications of these new findings in health and disease and speculate on the potential new roles of nucleosides and nucleic acids in energy metabolism.

Highlights

Nucleosides and nucleic acids are abundant in our diet, but their nutritional value has been poorly investigated.

Nucleosides maintain the viability of cells and organs when glucose is limited.

Specific nucleoside phosphorylases, including uridine phosphorylase 1/2 (UPP1/2), thymidine phosphorylase (TYMP), and purine nucleoside phosphorylase (PNP), catalyze nucleoside cleavage and release of the ribose moiety, which can enter the glycolytic pathway, thus fueling central carbon metabolism.

UPP1/2 integrate genetic and environmental signals to regulate uridine catabolism.

Energy production from nucleosides has major implications for metabolism, immunity, and cancer.

A 60+-year mystery solved

During the 1950s, by performing perfusion experiments using a simplified blood solution, Geiger and collaborators explored the nutritional requirements of the feline brain isolated from the rest of the circulation [1,2]. While simplified blood was only able to maintain brain activity for a short time, this period could be extended to a few hours when the liver was present in the circulation, suggesting the presence of liver-derived beneficial compounds. Two such compounds were found to be uridine and cytidine, both **pyrimidine** (see Glossary) **nucleosides** with a well-established role in **nucleic acid** synthesis. When added to simplified blood, uridine and cytidine were able to maintain brain electrical activity as well as corneal and pupillary reflexes for several hours [2].

Two decades later, in a series of landmark papers, Kennell and collaborators used nutrient supplementation to explore the nutritional requirements of cancer cells [3–5]. As expected, dietary sugars, such as glucose and fructose, could restore growth in otherwise 'sugar-free' conditions. However, the authors also reported that selected nucleosides, including uridine, were able to rescue cancer cell proliferation as effectively as glucose. Kennell *et al.*'s observations have since been confirmed by others in both primary and cancer cells [6–8] although the mechanism of rescue remained unclear.

Recently, research has focused on the beneficial effects of nucleosides and has provided a plausible rescue mechanism, arguing that nucleosides can support cell proliferation in sugar-limited conditions because they contain a ribose sugar moiety that can be salvaged for energy production (Figure 1) [9–12]. Nucleosides, such as uridine, inosine, and thymidine, can be catabolized by **nucleoside phosphorylases,** namely uridine phosphorylases 1 and 2 (UPP1/2), **purine** nucleoside phosphorylase (PNP), and thymidine phosphorylase (TYMP), respectively, to generate **ribose-1-phosphate (R1P)** or deoxyribose-1-phosphate (both referred to here as R1P). It is now becoming clear that R1P is then converted into **ribose-5-phosphate (R5P)** by a phosphoglucomutase and can be assimilated into the **pentose phosphate pathway (PPP)** to

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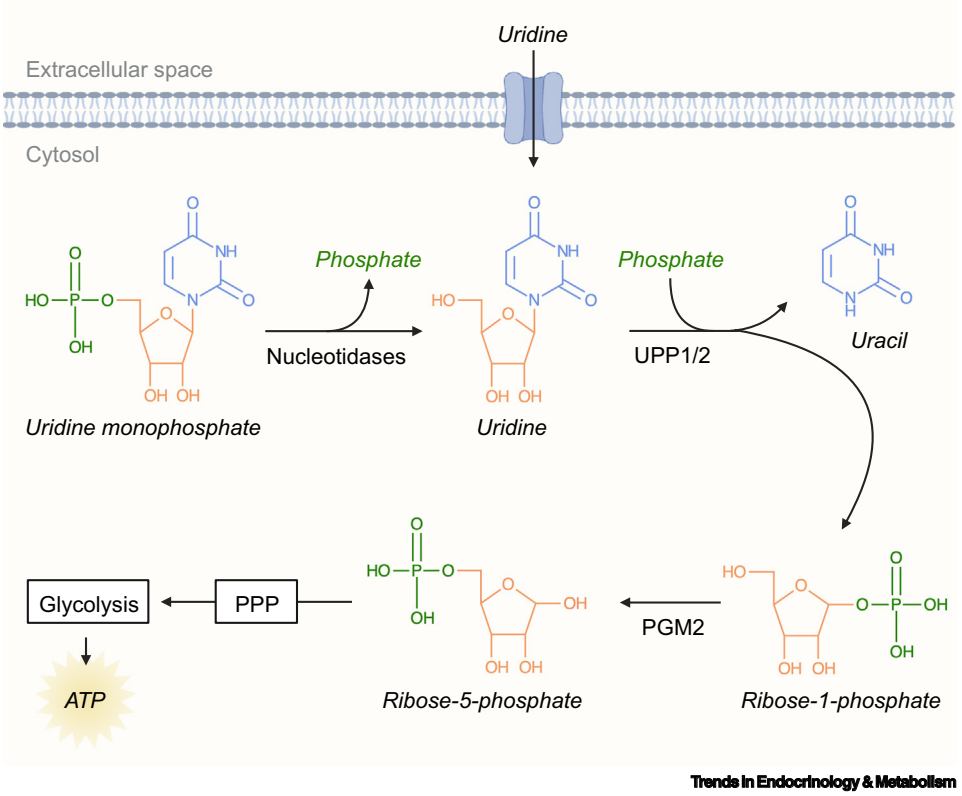

Figure 1. Uridine catabolism for energy production. Uridine is available from the circulation or from the degradation of its nucleotide monophosphate through the actions of a large family of phosphatases called nucleotidases. In catabolism, the nucleoside phosphorylases uridine phosphorylase (UPP)-1/2 use inorganic phosphate to split uridine into its component **nucleobase** (uracil) and phosphorylated sugar (ribose-1-phosphate; R1P). R1P is then converted into ribose-5-phosphate (R5P) by the phosphoglucomutase phosphoglucomutase-2 (PGM2), and can be processed through the pentose phosphate pathway (PPP), leading to its participation in lower glycolysis and ATP generation. Other purines and pyrimidines are catabolized in a similar way, although they may rely on different nucleoside phosphorylases. Green indicates phosphate groups; orange indicates ribose sugars; and blue indicates nucleobases. Figure created using BioRender (biorender.com).

fuel glycolysis and central carbon metabolism (Figure 1). Given the recent advances in research on nucleoside **catabolism** and its beneficial effects for health, we discuss here the current state of the field and potential implications of the latest discoveries.

Every day, we eat grams of nucleosides

The human diet comprises macromolecules, such as carbohydrates, proteins, lipids, and nucleic acids [13–18]. Nucleic acid content varies widely across food types and is highest in meats, cruciferous vegetables, mushrooms, fermented foods, and milk products, where they represent up to 10% of dry weight [17–20]. Accordingly, daily intake of nucleic acids or their constituents is estimated to measure in grams for humans (Figure 2, Key figure) [13]. **Nucleotides** and nucleosides are enriched in breast milk [20], where they represent an important nonprotein source of nitrogen and are needed for the correct maturation of the intestinal tissue, gut-associated immune system, and nervous system in the infant [21].

Despite their omnipresence, few studies have explored the dietary importance of nucleic acids and related molecules in adults. Research has also been limited regarding the absorption of

Glossary

Catabolism: metabolic process of breaking down complex molecules into simpler ones, usually accompanied by a release of energy.
Nucleic acids: macromolecules comprising nucleotides (e.g., DNA and RNA).
Nucleobase: nitrogen-containing compound used to generate nucleic acids, also called 'nitrogenous base' (e.g., uracil).
Nucleoside: compound combining a nucleobase and a five-carbon sugar (ribose or 2'-deoxyribose) (e.g., uridine).
Nucleoside phosphorylase: enzyme that uses inorganic phosphate to mediate the reversible conversion of a nucleoside into its nucleobase and ribose-1-phosphate or deoxyribose-1-phosphate.
Nucleotide: compound comprising a nucleoside linked to one to three phosphate group(s) (e.g., uridine monophosphate).
Pentose phosphate pathway (PPP): metabolic pathway that runs parallel to glycolysis and produces important precursors for nucleic acid and fatty acid synthesis, such as ribose-5-phosphate and NAD(P)H.
Purine: family of nucleobases comprising two carbon-nitrogen ring structures (e.g., adenine).
Pyrimidine: family of nucleobases comprising a single carbon–nitrogen ring structure (e.g., uracil).
Ribose-1-phosphate (R1P): metabolite comprising a ribose (five-carbon) sugar associated with a phosphate group in the 1′ position.
Ribose-5-phosphate (R5P): metabolite comprising a ribose (five-carbon) sugar associated with a phosphate group in the 5′ position.

Key figure

Current knowledge and open questions in nucleoside metabolism

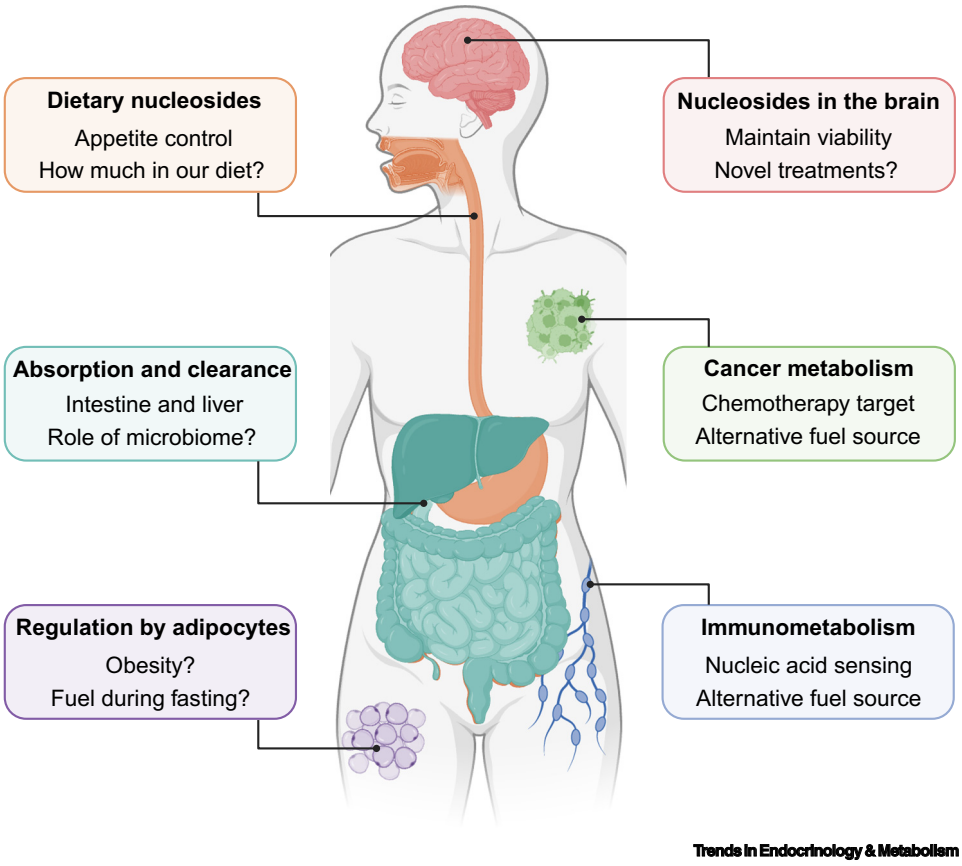

Figure 2. Nucleoside catabolism can impact many tissues of our body and many of its effects are only just beginning to be discovered. Figure created using BioRender (biorender.com).

dietary nucleic acid constituents, and how these processes may be affected by the microbiome (Figure 2). Feeding experiments using radiolabeled nucleic acids in mice showed that DNA and RNA were rapidly absorbed by intestinal cells as nucleosides, most of which were released into the systemic circulation (Figure 2) [22]. Eight hours after feeding, the majority of absorbed nucleosides had been degraded and excreted [22]. However, over the 4 h directly following ingestion, absorbed nucleosides could be found in various tissues, although only a minor fraction was incorporated into genetic material, mainly in the gut and liver [22]. At these earlier time points, feeding with larger amounts of dietary nucleic acids resulted in higher levels of nucleotides and nucleosides in tissues [22]. Along the same lines, a study in healthy volunteers who ingested uridine monophosphate (0.5–1 g) also found rapid absorption and an increase in circulating uridine [23].

Our bodies regulate the amount of circulating uridine mainly by promoting clearance by the liver (Figure 2) [24]. Following a meal, when glucose and other nutrients are abundant, uridine is rapidly

cleared and levels in plasma drop to the low micromolar (Table 1) [23,24]. However, in fasting conditions, uridine is released by adipocytes and its circulating levels increase to more than double compared with the basal level [23,24]. In healthy volunteers, higher levels of circulating uridine during fasting correlate with hunger and subsequent caloric intake (Figure 2) [23]. Recently, it was shown that uridine catabolism by its phosphorylases UPP1/2 generates R1P, which is subsequently converted into R5P and can be incorporated into the PPP and lower glycolysis [9,10]. Thus, uridine can participate in energy metabolism and represents an additional substrate for catabolism during times of nutrient scarcity (Figure 2).

The effects of high levels of nucleosides have been studied using dietary supplementation [25–28]. Studies based on mouse obesity models found that oral uridine and cytidine supplementation resulted in less weight gain in animals maintained on a high-fat diet [25,26]. While uridine may be beneficial in this model, other studies on the long-term effects of uridine supplementation in mice found adverse effects, namely the development of fatty liver, prediabetes, and obesity [27,28]. Since uridine can activate the same energy-producing pathways as glucose [9,10], a diet rich in nucleosides could contribute to metabolic disorders, such as obesity and type 2 diabetes mellitus (Figure 2). Interestingly, while *Upp1*-overexpressing mice are generally healthy, they frequently show early signs of fatty liver disease [29]. By contrast, *Upp1*-knockout (KO) models, characterized by high levels of uridine in plasma and tissue, maintain good health and viability, and no adverse effects have been described [30]. However, uridine phosphorylase expression differs between mice and humans [9,10,31,32]. In addition, a *Upp2*-KO model has yet to be generated, and could be crossed with *Upp1*-KO mice to completely ablate UPP activity in the animal. As a result, the development and further study of new *in vivo* models will be needed to better understand the contribution of uridine catabolism to energy homeostasis.

The use of uridine and other nucleosides for energy metabolism raises questions about the regulation of their catabolism. Energetic processes in cells are carefully controlled; indeed, both glucose uptake and flux through glycolysis respond to changes in oxidative phosphorylation (OXPHOS) to maintain energy balance [33]. However, surprisingly, altering OXPHOS activity affects neither uridine import nor its flux through glycolysis [9]. Moreover, when cells are cultured with excess glucose to saturate glycolysis, uridine continues to participate as a substrate [9]. By entering downstream in the glycolytic pathway, uridine appears to bypass known regulatory

Table 1. Concentration, solubility, and phosphorylases of the ten major nucleosides

Nucleoside	Water solubility (g/L) [73]	Concentration			Phosphorylase
		Human blood (μM) [73]	Human breast milk (μM) [73]	Murine tumor interstitial fluid (μM) [10,37]	
Uridine	135	3.1–21.1	4.2–7.1	1.3–102.5	UPP1/2, TYMP
Thymidine	66.8	<0.1–0.2	–	0.2–16.4	
Cytidine	43.8	0.1–0.3	3.4–5.1	2.9–53.1	
Deoxyuridine	90.6	0.05–0.6	–	–	
Deoxycytidine	15.9	0.2	–	0.4–23.3	
Adenosine	14	0.1–5.7	3	–	PNP, LACC1
Guanosine	15.3	0.8	1	–	
Inosine	13.8	0.1–5	–	1–211	
Deoxyadenosine	10.7	–	–	–	
Deoxyguanosine	11.5	–	–	–	

steps. Thus, its constitutive input into glycolysis may represent an important contributing factor in metabolic disorders resulting from energy imbalance.

Immune cells catabolize nucleosides to defend the organism

Immune cells are highly dependent on energy supply and molecular building blocks, making their activation and function highly susceptible to nutrient deficiency [34]. Furthermore, nutrients are often scarce at the site of infection or in the TME [35–37]. Therefore, the availability of alternative energy sources, such as nucleosides, offers the promise of improved immune cell function in nutrient-limiting conditions (Figure 2). Nutrient screening has highlighted the role of inosine to sustain $CD8^+$ T cell proliferation, survival, and effector function in glucose-limited conditions [12]. Inosine supplementation *in vivo* increased the antitumor efficacy of selected immunotherapies [12], showing how nucleosides can counteract the metabolic restrictions of the TME to improve immune function.

Both uridine and guanosine nucleosides are required for toll-like receptor (TLR) 7 and 8 [38,39] signaling. These receptors recognize foreign nucleic acids following infection and induce a proinflammatory response (Figure 2). Their activation leads to NF-κB-dependent transcription of *UPP1/Upp1* (Box 1) and increased uridine catabolism [9]. Nucleoside phosphorylases may act as a safeguard mechanism against TLR7/8-mediated proinflammatory signaling by modulating uridine and guanosine levels. In addition, TLR-7/8 induction of *UPP1/Upp1* transcription implies a feedback loop in which catabolism is promoted when foreign nucleic acids are sensed. This process is relevant in phagocytes, where ingested nucleic acids could be used for energy production during an immune response.

In vitro studies revealed that nucleoside consumption in macrophages depends on their activation profile. Activated proinflammatory macrophages can consume nucleosides, depleting the local uridine concentration, while anti-inflammatory (interleukin 4-treated) and tumor-educated (cultured with conditioned media from a cancerous cell line) macrophages may instead produce

Box 1. Regulation of uridine phosphorylases

Transcriptional regulation of *UPP1*

UPP1 is regulated at the transcriptional level and, to date, several transcriptional regulators of *UPP1* have been reported.

In physiological conditions, vitamin D3 induces *UPP1* transcription, with intriguing interethnic differences [63,64] (Figure I).

During the immune response, *UPP1* transcription is also promoted by cytokines, such as tumor necrosis factor alpha (TNFα) [64,65] or interferon gamma (IFNγ) [64], and by bacteria-derived lipopolysaccharide (LPS) [9] as well as nucleic acid ligands [9]. These act through their own receptors and pathways, leading to activation of the transcription factors NF-κB, STAT-1, and IRF1 (Figure I) [65,66].

In cancers, oncogenic signaling pathways and transcription factors, such as MITF [9], KRAS-MAPK [10], and CBFβ-RUNX2 [67], also promote *UPP1* transcription (Figure I), and low glucose levels can also induce *UPP1* expression through the MAPK pathway in pancreatic ductal adenocarcinoma (PDA) [10]. To prevent aberrant *UPP1* expression, the tumor suppressor protein p53 binds the *UPP1* promoter and represses its activation (Figure I) [68]. How all these pathways are interconnected is not clear, but it is noteworthy that, in some cells, MITF and NF-κB can act downstream of KRAS-MAPK signaling, suggesting a common pathway [69,70].

UPP2: a redox sensor with low expression in humans?

UPP2 differs from UPP1 in its regulation. While UPP1 is regulated mainly at the transcriptional level, UPP2 is regulated post transcriptionally through a redox-sensitive disulfide bridge (Figure I) [71]. Recent work in mice showed that a reduced intracellular environment promotes Upp2 activity and uracil production, increasing energy expenditure and locomotor activity [72]. While the modulation of UPP2 and its redox state may hold promising therapeutic potential, most studies to date have centered around UPP1. This is probably because UPP2 levels are very low and often undetectable in humans [9,10,31], suggesting that, under physiological conditions, UPP1 is the primary uridine phosphorylase.

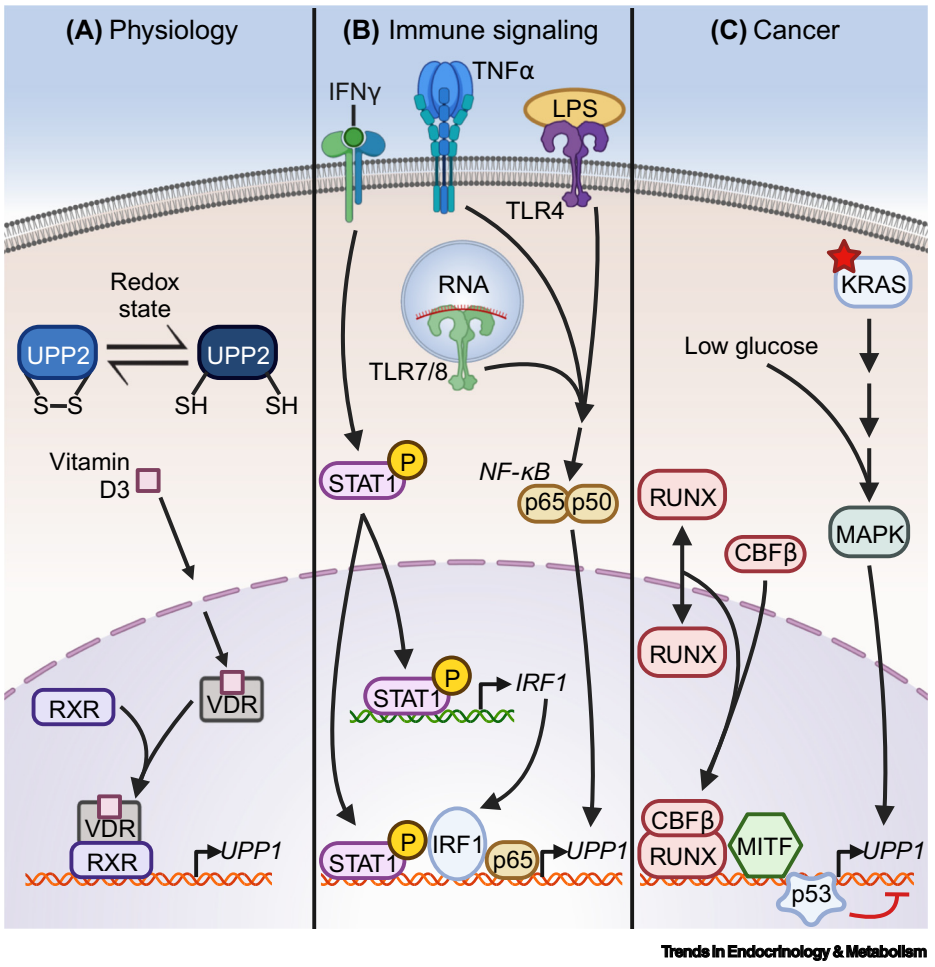

Figure I. Regulation of uridine phosphorylases. Uridine phosphorylases 1/2 (UPP1/2) are regulated transcriptionally and post-translationally, respectively. In physiological conditions (A), but also in cancer (B) or during an immune response (C), signaling pathways and transcription factors are the main regulators of UPP1 and uridine consumption. Abbreviations: CBFβ, core binding factor beta subunit; IFNγ, interferon gamma; IRF1, interferon regulatory factor 1; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; MITF, microphthalmia-associated transcription factor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; RUNX, runt-related transcription factor 1; RXR, retinoid X receptor; STAT1, signal transducer and activator of transcription 1; TLR, toll-like receptor; TNFα, tumor necrosis factor alpha; VDR, vitamin D receptor. Figure created using BioRender (biorender.com).

and release uridine [10,40], potentially providing fuel for cancer cells. However, macrophage depletion in mice did not affect uridine levels in the tumor interstitial fluid, although it caused a strong decrease in plasma levels [10]. These unchanged amounts of uridine in the TME are not consistent with the observed release of nucleosides by tumor-educated macrophages. Thus far, *in vitro* experiments have been performed in the presence of large amounts of glucose [40]. Since cleavage of uridine into uracil and R1P is reversible, the abundance of glucose may influence R1P levels and dictate the directionality of the UPP1/Upp1 reaction. The factors regulating uridine abundance and consumption in the TME are complex [10] and require further investigation. The development of *in vivo* models to study nucleoside phosphorylases will offer a more physiologically relevant context for studying their role in the immune system.

Several mouse models are available to study the role of nucleoside phosphorylases. For example, knockout models of *Tymp* and *Pnp* have been used to study human disease-associated mutations, which, in the case of *PNP*/*Pnp*, results in immunodeficiency [39,41–43]. Since different immune cells or other cell types display different preferences for specific nucleosides, lineage-specific transgenic models could prove highly informative. These mouse models, combined with dietary nucleoside supplementation, will allow a better understanding of the contribution of nucleosides and nucleic acids during the immune response.

Nucleosides fuel cancers

The TME is characterized by limited nutrients, including glucose, leading to competition between cells [37,44]. At least three nucleosides (uridine, inosine, and thymidine) can be catabolized and channeled into glycolysis to fuel cancer cell proliferation (Figure 2) [9–12]. Nucleoside catabolism is dependent on expression of the corresponding nucleoside phosphorylase (Table 1, Box 1). High *TYMP* expression in tumors promotes cancer cell growth [11,45–47]. Similarly, in cells derived from adenocarcinoma or rhabdomyosarcoma lineages, inosine supplementation allows growth in the absence of glucose [12]. Uridine, the most soluble and most abundant plasma nucleoside (Table 1), can also be used as a carbon source for glycolysis in nutrient-limiting conditions [9,10]. Growth on uridine correlated strongly with *UPP1* levels across 482 cancer cell lines from 22 cancer lineages, in particular melanoma and glioma. These results were confirmed in a panel of nine melanoma [9] and 12 pancreatic ductal adenocarcinoma (PDA) cell lines [10], in which genetic ablation of *UPP1* completely abolished uridine catabolism and uridine-dependent cell growth [9,10]. Patients with high *UPP1* expression in cancers from diverse origins, including PDA, present shorter life expectancies [10,48]. Consistent with this, genetic ablation of *Upp1*/*UPP1* in both mouse PDA allografts [10] and human colorectal cancer xenografts [49] reduced tumor growth. Taken together, these data underline the importance of nucleoside phosphorylases and nucleoside catabolism for cancer cell proliferation. Importantly, while *in vivo* experiments with nucleoside phosphorylase-KO models have highlighted the importance of these enzymes in cell proliferation, the role of nucleosides themselves in cancer remains to be clarified. This could be investigated by using nucleoside-rich diets or intratumoral nucleoside injections.

The nucleoside phosphorylases UPP1 and TYMP have important roles in the metabolism and efficacy of fluoropyrimidine-based chemotherapies. Fluoropyrimidines, such as 5-fluorouracil (5-FU) and capecitabine, disrupt DNA synthesis and inhibit cancer cell growth [50,51]. UPP1 and TYMP use R1P to catalyze the conversion of 5-FU into active cytotoxic metabolites [51,52]. Therefore, nucleoside phosphorylase expression and activity levels can impact the response to fluoropyrimidine therapy and influence treatment outcomes [49,53]. Moreover, since these reactions use R1P, a product of glucose metabolism, their directionality can be influenced by glucose availability. Depletion of R1P could limit the conversion of 5-FU into cytotoxic metabolites and, hence, restrict the efficacy of fluoropyrimidine-based chemotherapies. Overall, a better understanding of the role of nucleoside metabolism in cancer has the potential to not only improve current therapies, but also identify new antitumoral strategies (Figure 2).

Treating neurological disorders with nucleosides?

Pyrimidine nucleosides are consumed by the brain in nutrient-limiting conditions (Figure 2) [7,8], and uridine supplementation has been used to treat neurological disorders caused by rare mutations in *de novo* pyrimidine synthesis enzymes [Mendelian Inheritance in Man (MIM): #258900 and #616457] [54,55]. Orally administered uridine triacetate (Xuriden™ and Vistogard™) can enter the brain through multiple nucleoside transporters expressed at the blood–brain barrier [56] and provides a substrate for pyrimidine salvage pathways. Since the salvage pathway restores

the production of pyrimidines, uridine triacetate treatment can alleviate most developmental and neurological symptoms [54,55].

Recent findings on the use of nucleosides as a possible energy source able to bypass upper glycolysis [9] may extend the current applications of this established and successful treatment. Notably, supplementing with uridine could be beneficial in cases of nutrient starvation in the brain, for example following stroke or ischemia (Figure 2) [7,8,56]. In addition, it has been suggested that nucleoside supplementation could be beneficial in disorders caused by defective intracellular glucose uptake (Figure 2) [9]. GLUT1 Deficiency Syndrome [MIM #606777] is a rare genetic disorder characterized by malfunction of the GLUT1 transporter, resulting in the failure of glucose to enter red blood cells and the brain. This disorder affects cognitive and motor functions and can result in seizures [57,58]. Currently, patients are treated with a ketogenic diet to remove the reliance of the brain on glucose, providing ketones as an alternative energy source. This treatment has reduced seizures and motor-related symptoms, but it does not fully resolve cognitive symptoms [59,60]. As an alternative, nucleoside treatment would be expected to restore glycolytic intermediates, which would be lacking with ketone treatment, and, therefore, may improve the entire range of symptoms that accompany this syndrome. Accordingly, oral treatments for supplementing nucleosides or modulating their metabolism could provide safe, non-invasive, and effective options to improve patient quality of life in multiple situations.

Concluding remarks and future perspectives

Nucleosides have traditionally been recognized primarily for their role in nucleic acid synthesis. However, recent studies have highlighted their potential as alternative energy sources, particularly when glucose is scarce [9–12]. This newfound role for nucleosides relies on the activity of nucleoside phosphorylases, which cleave nucleosides to provide a ribose group that can fuel lower glycolysis and, thus, ensure energy production, even in the absence of glucose.

These findings on nucleoside catabolism open new insights into their potential role in health and disease (see Outstanding questions). Some cancers can use nucleosides to produce energy and sustain their growth when nutrients are limited [9–12]. While nucleotide synthesis inhibitors have been extensively investigated, there is still considerable potential for novel inhibitors of nucleoside catabolism. Some of these inhibitors are already clinically approved, such as trifluridin and tipiracil for TYMP [61], while others, such as the UPP1 inhibitor TK-112690, are in clinical trials. These molecules may open new avenues for anticancer treatments and could complement existing therapies. However, it is important to consider the beneficial effects of nucleoside consumption by other cells in the TME, most notably immune cells. For example, T cells can use inosine to sustain their energy demands and antitumoral activity [12]. Furthermore, macrophages may also rely on nucleosides, including those phagocytosed, as an energy source to sustain their immune activity [9]. The development of comprehensive *in vivo* models, including cell type-specific models, will be required to investigate more fully how nucleoside catabolism in different cell types can impact the interplay between cancer and the immune system within the TME.

Healthy tissues and cells may also be affected by the nucleosides that we consume daily. Since these molecules can promote glycolysis, bypassing key regulatory steps [9], they may contribute to metabolic disorders, such as fatty liver and obesity. Thus, better knowledge of the genetic material we consume, how it is used, and how it contributes to metabolic disorders will be key to addressing many diverse issues important for public health. Furthermore, nucleosides released upon fasting may represent a novel source of energy for cells in times of scarcity. RNA and ribosomes are known to be degraded upon starvation [62], suggesting that, similar to glucose stored in glycogen and starch, the nucleosides polymerized into RNA represent a reserve of stored energy.

Outstanding questions

What amount of nucleic acids, nucleotides, and nucleosides do we consume in our diet?

Do dietary nucleosides participate in metabolic disorders?

Which immune cells catabolize nucleosides, and how does this impact their function?

How is nucleoside abundance and consumption regulated in the TME? Can we target nucleoside consumption to promote an antitumoral immune response?

Besides UPP1/2, how are the other nucleoside phosphorylases regulated?

Similar to starch and glycogen, can RNA, a polymer of nucleosides, provide a means of energy storage? If so, could ribophagy provide energy to cells?

Could nucleosides offer a treatment strategy for disorders arising from impaired glucose catabolism?

Will nucleoside phosphorylase inhibitors prove to be efficient therapies? Could these small molecules be used as immune modulators or anticancer agents, or to prevent obesity from excessive nucleoside absorption?

Our evolving comprehension of nucleoside and nucleoside phosphorylase biology has reshaped the conventional view that these molecules simply provide building blocks for genetic material. Nucleosides emerge as vital players in energy metabolism, with far-reaching implications for health and disease. Future research will shed more light on the role of nucleoside catabolism in the fields of immunology, tumor biology, and energy metabolism, with potential applications for therapeutic interventions.

Acknowledgments

We thank Mads Foged, Marcell Harhai, Miriam Lisci, Kinsey Maundrell, and Emeline Recazens for their critical comments on this work. This work was supported by the Swiss National Science Foundation (project grant 310030_200796).

Declaration of interests

A.A.J. has filed a provisional patent application related to nucleotide catabolism inhibition. The other authors declare no competing interests.

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