Deoxyribonucleotide Triphosphate Metabolism in Cancer and Metabolic Disease

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The maintenance of a healthy deoxyribonucleotide triphosphate (dNTP) pool is critical for the proper replication and repair of both nuclear and mitochondrial DNA. Temporal, spatial, and ratio imbalances of the four dNTPs have been shown to have a mutagenic and cytotoxic effect. It is, therefore, essential for cell homeostasis to maintain the balance between the processes of dNTP biosynthesis and degradation. Multiple oncogenic signaling pathways, such as c-Myc, p53, and mTORC1 feed into dNTP metabolism, and there is a clear role for dNTP imbalances in cancer initiation and progression. Additionally, multiple chemotherapeutics target these pathways to inhibit nucleotide synthesis. Less is understood about the role for dNTP levels in metabolic disorders and syndromes and whether alterations in dNTP levels change cancer incidence in these patients. For instance, while deficiencies in some metabolic pathways known to play a role in nucleotide synthesis are pro-tumorigenic (e.g., p53 mutations), others confer an advantage against the onset of cancer (G6PD). More recent evidence indicates that there are changes in nucleotide metabolism in diabetes, obesity, and insulin resistance; however, whether these changes play a mechanistic role is unclear. In this review, we will address the complex network of metabolic pathways, whereby cells can fuel dNTP biosynthesis and catabolism in cancer, and we will discuss the potential role for this pathway in metabolic disease.

Keywords: purines, pyrimidines, c-Myc, p53, mTORC1, diabetes, obesity

INTRODUCTION

The maintenance of deoxyribonucleotide triphosphate (dNTP) pools is critical for multiple cellular pathways. For instance, imbalances in dNTPs are associated with genomic instability (1). Likewise, they have also been shown to disturb mitochondrial DNA (mtDNA) and consequently mitochondrial fitness, which may lead to mitochondrial diseases (MDs), such as diabetes, obesity, and cancer (2). Additionally, disorders of purine and pyrimidine metabolism (DPPM) profoundly affect cell metabolism, underlying the importance of nucleotides for cell behavior (3). Thus, both nucleotide synthesis and degradation must be exquisitely fine-tuned. In this review, we will focus on synthesis of dNTPs and the consequences of dNTP pool imbalances in cancer and MDs.

HEALTHY dNTP POOLS

A correct balance of dNTPs is necessary for the prevention of multiple pathologies. A healthy cell must maintain two asymmetric and spatial-temporal dNTP pools; one for nuclear DNA synthesis and repair and another for mtDNA replication and repair. Disruptions in dNTP balance are associated with enhanced mutagenesis, leading to genomic instability, which promotes cancer (4), and may have a role in metabolic disease (5).

Cytosolic dNTP pool concentrations positively correlate with the cell cycle. In fact, the amount of dNTPs at the beginning of S-phase is not enough for a complete DNA duplication (6). The S-phase increase in dNTPs is necessary for faithful nuclear DNA replication. mtDNA is replicated continuously in post-mitotic cells, and faithful maintenance of mtDNA also depends on correctly balanced dNTPs (7). Thus, both proliferating and non-proliferating cells need to fine-tune nucleotide and dNTP synthesis to allow for both nuclear and mtDNA replication and repair to maintain the health of the cell.

Anabolism and Catabolism of Nucleotides

Cells possess two biosynthetic pathways to produce dNTPs: de novo and salvage (8). Purines and pyrimidines arise from two different de novo pathways that generate nucleotides starting from raw material (glucose, glutamine, aspartate, and HCO₃) (9). The de novo nucleotide synthesis pathway is highly energy-intensive (9). Therefore, cells have developed a more energy-efficient route to synthesize nucleotides, termed the salvage pathway (10). The salvage pathway acts as a recycling plant taking free nitrogen bases and nucleosides arising from nucleic acid breakdown and diet (9). Nucleosides are hydrophilic compounds, thus proper function of nucleoside transporters (SLC29 and SLC28 families) is an essential requirement for salvage pathway function (11). Ribonucleotides obtained by either pathway can be reduced to their deoxyribonucleotide counterpart in a reaction catalyzed by ribonucleotide reductase (RNR) (12).

Turnover of RNA and other nucleotides occurs regularly to maintain homeostasis. Human cells cannot break down the purine ring. Purine catabolism involves a sequence of three reactions in which nucleotides are stripped step-by-step from their phosphates and sugar to finally become oxidized to the end product uric acid (UA), which is excreted into the urine (13). Conversely, uracil and thymidine rings can be completely degraded to β-alanine and β-aminoisobutyrate, respectively. Subsequently, both metabolites can be excreted or transformed into intermediates of the tricarboxylic acid (TCA) cycle (14). Biosynthesis and catabolism of nucleotides and dNTPs are highlighted in **Figure 1**.

IMPAIRED NUCLEOTIDE METABOLISM IN CANCER AND METABOLIC DISEASE

Deregulation of nucleotide metabolism is associated with a broad spectrum of pathological conditions, including cancer and MDs (15–17). Virtually all metabolic pathways have been implicated in dNTP biosynthesis. Thus, de novo and salvage pathways, as well as all involved anapleurotic reactions (**Figure 1**), need to be highly cross-regulated.

It is well known that cancer cells must increase dNTP biosynthesis (18) to ensure rapid replication of the genome (17). This occurs through a variety of pathways (discussed below). In contrast, MDs are caused by congenital or acquired genetic defects in metabolic enzymes. DPPM are due to abnormalities in the biosynthesis, interconversion, and degradation of nucleotides (19). DPPM have a wide variety of clinical presentations, highlighting the importance of proper nucleotide metabolism for cell and

organism function (15). Alterations in nucleotide metabolism are also present in other metabolic-related pathological conditions, such as diabetes, obesity, and insulin resistance (20–22) (**Table 1**). In this section, we will summarize some important features affecting nucleotide metabolism in cancer and MDs.

Deregulation of Major Growth Signaling Pathways Leads to Nucleotide Pool Imbalances in Cancer and Metabolic Disease

The main growth signaling pathways (PI3K-AKT and ERK1/2-MAPK) are induced and maintained during metabolic reprogramming of cancer (18). Additionally, deregulation of these pathways may contribute to different MDs, including diabetes, obesity, or steatosis resistance (33, 89, 90). These pathways sense and orchestrate nutrient utilization; therefore, is not surprising that alterations in these pathways affect energy and biomass production and cause a broad variety of diseases.

mTOR is a central signaling pathway that integrates environmental inputs (e.g., nutrients and hormones) into downstream pathways to control many cellular processes (91). This includes regulation of metabolism, growth, and survival (32). Indeed, the mTORC1/2 pathway not only promotes glucose uptake and protein and lipid biosynthesis, but also promotes nucleotide biosynthesis (29, 30) and uptake of nucleosides through transporters (88). At least one member of this pathway is altered in 38% of human cancer (92). Altered metabolism induced by aberrant mTORC1 activation has also been shown to play a role in diabetes and obesity (32, 93).

c-Myc, one of the most commonly altered proteins in human cancer, is also regulated by PI3K-AKT and ERK1/2-MAPK pathways (94). c-Myc is a highly pleiotropic transcription factor considered a master regulator of cell metabolism (34, 35) through regulation of glycolysis, glutamine metabolism, and mitochondrial biogenesis (95, 96). Indeed, c-Myc has been shown to induce hepatic glucose uptake and utilization, while blocking gluconeogenesis and ketogenesis, suggesting a counteracting effect of c-Myc in obesity and insulin resistance (36, 97). In addition to regulating glucose and glutamine, substrates for purine and pyrimidine biosynthesis (**Figure 1**) (98), c-Myc also transcriptionally regulates nucleotide metabolic enzyme gene expression (35). Thus, deregulation in c-Myc acutely alters nucleotide homeostasis in cancer (99), and it is interesting to speculate that the role of c-Myc in MDs is also related to nucleotide metabolism.

Previous publications from our laboratory and others have shown that DNA damage and DNA damage response (DDR) proteins regulate dNTP biosynthesis in the context of cancer (80, 100, 101). Interestingly, upregulation of p53, a key player in the DDR, in adipose tissue is associated with increased inflammation and insulin resistance (102). Notably, wild-type p53 negatively regulates G6PD activity (37), the rate-limiting enzyme of the pentose phosphate pathway and one of the most important sources of nucleotides (103). Upregulation of G6PD correlates with functional defects in liver, heart, and pancreas of obese and diabetic animals (104). Although the relationship between G6PD upregulation and increased oxidative stress has been studied in MD (105), the implication for nucleotide metabolism has not
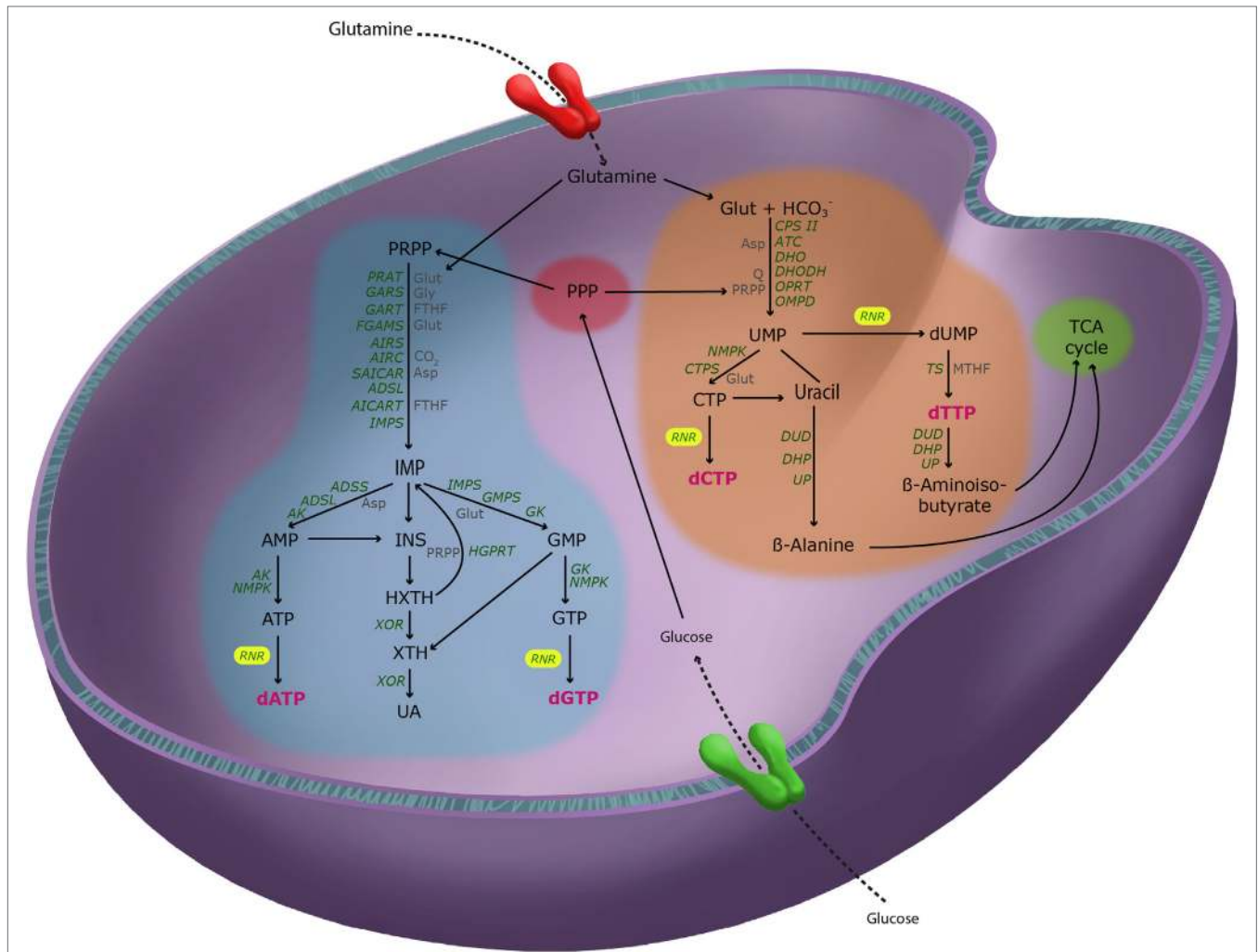
FIGURE 1 | Pathways of deoxyribonucleotide metabolism in mammalian cells. Simplified representation of purine (blue) and pyrimidine (orange) metabolism and their crosstalk with the major metabolic pathways, the pentose phosphate pathway [(PPP), red] and the tricarboxylic acid cycle (green). Key metabolic enzymes (green), their principal reactive substrates (gray), and the four deoxyribonucleotide triphosphate (dNTP) end-products (magenta) are shown. Glucose and glutamine feed into both purine and pyrimidine metabolism to donate carbons and nitrogens to all dNTPs. Abbreviations: RAT, phosphoribosylpyrophosphate amidotransferase; GARS, glycinamide ribonucleotide synthetase; GART, glycinamide ribonucleotide transformylase; FGAMS, phosphoribosylformyl-glycineamide synthetase; AIRS, phosphoribosylaminoimidazole synthetase; AIRC, phosphoribosylaminoimidazole carboxylase; SAICAR, phosphoribosylaminoimidazole-succinocarboxamide; ADSL, adenylosuccinate lyase; AICART, phosphoribosylaminoimidazolecarboxamide formyltransferase; IMPS, inosine monophosphate synthase; ADSS, adenylosuccinate synthetase; AK, adenylate kinase; NMPK, nucleotide monophosphate kinase; IMPS, inosine monophosphate dehydrogenase; GMPS, guanosine monophosphate synthetase; GK, guanylate kinase; XOR, xanthine oxidoreductase; HGPRT, hypoxanthine–guanine phosphoribosyltransferase; RNR, ribonucleotide reductase; CPS II, carbamoyl phosphate synthetase II; ATC, aspartate carbamoyltransferase; DHO, dihydroorotase; DHOD, dihydroorotase dehydrogenase; OPRT, orotate phosphoribosyltransferase; OMPD, orotidine monophosphate decarboxylase; CPTS, cytidine triphosphate synthetase; TS, thymidylate synthase; DUD, dihydrouracil dehydrogenase; DHP, dihydropyrimidinase; UP, ureidopropionase; Glut, glutamine; Gly, glycine; FTHF, $N10$-formyltetrahydrofolate; Asp, aspartate; PRPP, phosphoribosylpyrophosphate; Q, ubiquinone; MTHF, $N5,N10$-methylenetetrahydrofolate.

yet been addressed. More research is needed to understand the contribution of dNTP imbalances due to G6PD deregulation in diabetes and obesity.

An imbalance in nucleotides has been shown in two different studies related to diabetes (106, 107). Additionally, pyrimidine metabolism has been linked to fatty liver (26). Interestingly, increasing evidence suggests a link between obesity, a risk factor for non-alcoholic fatty liver disease (108), and cancer. Obese patients show many cancer-promoting features, such as chronic low-level inflammation (109), insulin-resistance/

diabetes (110), and deregulation of mTORC1 (111). Although the contribution of deregulated nucleotide pools promoting cancer has been extensively demonstrated (18, 112–115), their role in MD and metabolic-related diseases has not yet been elucidated. Based on these recent studies, we speculate that deregulation of nucleotide pools may in part contribute to the altered metabolic landscape promoting obesity and diabetes. Studying the implications of altered nucleotide pools in these diseases would open a therapeutic window based on modulation of nucleotide metabolism.

TABLE 1 | Genes, protein families, and pathways discussed in this review: role in deoxyribonucleotide triphosphate (dNTP) metabolism and expression in cancer and metabolic disease.

Gene/family/ pathway	Known role in dNTP metabolism	Expression in cancer	Expression in metabolic disease
Purine/pyrimidine synthesis pathway	Necessary for *de novo* dNTP biosynthesis (8)[a]	Increased (23) or mutated (24, 25)	Heptatic steatosis (uridine metabolism) (↓) (26) Diabetes[b] (↓) (27)
MTOR	Promotes glucose uptake (28); promotes *de novo* nucleotide biosynthesis (29, 30)	Increased (31)	Diabetes (↑) (32) Obesity (↑) (33)
MYC	Induces glucose uptake and utilization (34); transcriptionally regulates nucleotide metabolic enzymes (23, 35)	Increased (oncogene) (23)	Insulin resistance (↑)[c] Obesity (↑)[c] (36)
TP53	Negative regulator of pentose phosphate pathway through G6PD (37); gain-of-function mutations increase gene transcription of genes for dNTP synthesis (38)	Decreased or mutated (tumor suppressor) (39)	Insulin resistance (↑) Glucose intolerance (mut) (5) Mitochondrial changes (mut)[d] (40)
PI3K-AKT pathway	Oncogenic activation promotes glucose and glutamine uptake and catabolism (41)	Increased (oncogenes) (41)	Diabetes (↑) (42) Nonalcoholic fatty liver disease (↑) (43) Obesity (↑) (44)
ERK-MAPK pathway	Regulation of CPS II in *de novo* pyrimidine synthesis (45)	Increased (oncogenes) (46)	Diabetes (↑) (47) Obesity (↑) (48)
G6PD	Rate-limiting for ribose-5-phosphate synthesis from the PPP (49)[a]	Increased or mutated (50)	Obesity (↑) (51) Diabetes (↑) (52)
RRM1	Catalytic subunit of the ribonucleotide reductase (RNR); catalyzes the reduction of deoxyribonucleotides from ribonucleotides (12)[a]	Increased or decreased (53)	Unknown
RRM2	Regulatory subunit of RNR (12); S-phase regulated (54); rate-limiting enzyme in the reduction of deoxyribonucleotides from ribonucleotides (55)[a]	Increased (oncogene) (53)	Unknown
RRM2B	Regulatory subunit of the RNR (56); formation of deoxyribonucleotides from ribonucleotides for DNA damage repair and mitochondrial DNA (mtDNA) replication (57–59)[a]	Increased or decreased (53)	Mitochondrial disorders (↓) (60)
SLC25 family	Mitochondrial nucleoside transporters (61) Important for mtDNA pools through the salvage pathway (62)	Increased (63)	Mitochondrial disease (mut)[e] Mitochondrial dysfunction (↓)[f] (61)
SLC29 and SLC28 families	Nucleoside transporters that are important for the salvage pathway (11, 64, 65)	Increased (11)	Diabetes (mut)[g] (66)
TK2	Phosphorylates deoxycytidine to generate dCTP (67)	Unknown	Mitochondrial disease (↓) (68)
DGUOK	Catalyzes the conversion of deoxyguanosine to dGMP (67)[a]	Mutated[h] (69, 70)	Mitochondrial disease (mut) (69)
TWNK	Mitochondrial helicase (71)	Unknown	Mitochondrial dysfunction (mut) (72, 73)
POLG	Catalytic subunit of the mitochondrial DNA polymerase (74)	Mutated (75–77)	Mitochondrial disease (mut) (77–79)
Ataxia-telangiectasia mutated	Increases glucose/glutamine uptake and inhibits the PPP (80)	Mutated (81)	Mitochondrial dysfunction (mut)[i] Insulin resistance (mut)[i] (82)
XOR	Catalyzes the conversion of xanthine to uric acid (83)[a]	Increased[j] or decreased (84)	Metabolic syndrome (mut)[k] Insulin resistance (mut)[k] Diabetes (mut)[k] Fatty liver disease (mut)[k] (85)

[a]*These genes/pathways are shown in* **Figure 1**.

[b]*These studies show that purines and pyrimidines are downregulated in diabetes. It is not known whether changes in purine or pyrimidine synthesis genes are the mechanism behind this observation.*

[c]*Increased MYC expression counteracts insulin resistance and obesity.*

[d]*Occurs in patients with Li–Fraumeni syndrome.*

[e]*SLC25A4 (86).*

[f]*SLC25A33 and SLC25A36 have only been tested in mouse models (87, 88).*

[g]*SLC29A3 is the only gene in this family that has been found to affect metabolic disease.*

[h]*While the data are limited, some patients with DGUOK mutations have hepatocellular carcinoma.*

[i]*Occurs in patients with ataxia-telangiectasia.*

[j]*Increased XOR expression/activity is likely important for cancer initiation; however, XOR expression is decreased in most established tumors.*

[k]*Occurs in patients with XOR deficiency.*

RNR in Cancer and Metabolic Disease

Ribonucleotide reductase reduces ribonucleotides to the corresponding deoxyribonucleotides (116, 117). In mammals, RNR is a tetrameric enzyme composed of two homodimeric subunits, RRM1 and RRM2. Whereas, RRM1 is continuously expressed throughout the cell-cycle, expression of RRM2 is activated upon entry into S-phase (54, 118). Additionally, RRM2 is rapidly degraded *via* the proteasome in G2 (12, 119). Thus, RRM2 is

considered rate-limiting for RNR activity. RRM2B (RNR subunit M2B) is an alternative M2 subunit that is induced by p53 activation in response to DNA damage (56). RRM2B is not cell-cycle regulated *per se*, but it plays key roles in enhancing dNTP synthesis in cells under stress (120–122) and mediating mtDNA synthesis and repair (57–59).

The role of RNR in cancer is clear as it was one of the first identified DNA damage-induced enzymes (123). While RRM2 overexpression is tumorigenic, leading to lung neoplasms *in vivo*, RRM1 reduces tumor formation, migration, and metastasis [reviewed in Ref. (53)]. Previous studies from our lab and others have shown the potential of RRM2 as a prognostic and diagnostic biomarker in multiple cancers (112, 124–127). However, the utility of RRM1 and RRM2B as a tumor biomarker is still unclear [reviewed in Ref. (53)].

Although there is no study directly linking RNR with MD, RRM2B is required for mtDNA synthesis and healthy mitochondrial function (57). Deregulated mitochondria are associated with a higher risk of diabetes and obesity (discussed below). Therefore, it is possible that RNR function is linked to these MDs (**Table 1**). More mechanistic studies will be needed to determine the role for RNR in obesity and diabetes.

Mitochondrial Dysfunction in dNTP Pool Disruption During Cancer and Metabolic Disease

The mitochondria are one of the most important organelles for eukaryotic function (128). In addition to the production of ATP through oxidative phosphorylation, mitochondria are also the scaffold of several metabolic reactions for cellular building block synthesis (e.g., fatty acid beta-oxidation, one-carbon/folate cycle, TCA cycle, amino acid metabolism, etc.) (129). Hence, altered mitochondrial behavior has a broad impact on cellular metabolism.

Maintenance of mitochondrial dNTP pools is critical for proper mtDNA function. Alterations in nuclear genes involved in transport of cytosolic dNTPs (e.g., SLC25A4), the salvage nucleotide biosynthesis in the inner mitochondrial membrane (e.g., TK2 and DGUOK), and genes involved in mtDNA replication (e.g., TWNK and POLG) are implicated in both cancer and metabolic syndromes (63, 68, 77–79, 130–133). Moreover, dysfunction in the electron transport chain induces oxidative stress, which has been associated with impaired one-carbon metabolism (134, 135), an essential anapleurotic pathway for both purine and pyrimidine nucleotides. Mitochondrial genomic instability due to increased levels of reactive oxygen species (ROS) and/or mutations in mtDNA or nuclear genes involved in mitochondria function are underlying factors of MDs, and contribute to cancer and diabetes (136). Alterations in genes discussed above that are important for dNTP homeostasis and mitochondrial function are highlighted in **Table 1**.

Although the link between mitochondrial dysfunction and MD has been studied for the past two decades, the results are contradictory (137). These contradictory results mainly arise from the complex relationship between mitochondria and metabolism, but also from the lack of global and standardized methodological

strategies to phenotype insulin-resistance in humans (138). Dysregulation of nucleotide metabolism is an important aspect of mitochondrial dysfunction; therefore, their role in MDs should not be ignored.

Relationship Between DPPM and Cancer

It is clear that cancer is a metabolic disease; however, a predisposition to cancer is not a foregone conclusion in patients with DPPM, who by definition have alterations in nucleotide supplies. Interestingly, while deficiencies in some metabolic pathways known to play a role in nucleotide synthesis are pro-tumorigenic, others confer an advantage against the onset of cancer. This highlights the large variability in the clinical presentation of these disorders.

Alterations in p53 or ataxia-telangiectasia mutated (ATM) lead to metabolic changes and predispose patients to cancer. Patients with germline *TP53* (encoding for p53) mutations have Li–Fraumeni syndrome and are predisposed to cancer (139, 140). Interestingly, a recent report showed that nucleotide metabolism is regulated by the gain-of-function activity of mutant p53 (38). Consistently, wild-type p53 negatively regulates G6PD and PPP activity to decrease dNTP synthesis (37). Similarly, our group has previously shown that ATM (mutated in some ataxia-telangiectasia patients) inactivation increases glucose uptake and enhances glucose flux through the PPP and ultimately increases dNTP biosynthesis (**Figure 1**) (80, 141). Indeed, patients with ATM mutations show alterations in glucose homeostasis (142, 143). It is well-known that these patients have an increased susceptibility to cancer (144). It is interesting to speculate that alterations in dNTP metabolism may play a role in the cancer predisposition in these patients; however, further studies are needed to support this notion.

Other DPPM confer a tumor suppressive benefit. For instance, patients with G6PD deficiency have a reduced risk of some cancers (145–147) (**Table 1**). This suggests that hyperactivity of dNTP synthesis is more likely to increase cancer risk than deficiencies in synthesis.

Finally, some DPPM have both a pro- and anti-tumorigenic effect. Deficiency in xanthine oxidoreductase (XOR), the enzyme that catalyzes the last step in purine catabolism (**Figure 1**), increases UA (148). There is a dual role for UA in cancer, the so-called the oxidant–antioxidant UA paradox (149). On one hand, extracellular UA is a potent ROS scavenger, thus protecting cells against oxidative stress (150). On the other hand, high intracellular levels of UA in a XOR-deficient cellular background promote dNTP biosynthesis and tumor growth by shuttling XOR precursors (xanthine and hypoxanthine) into the purine salvage pathway (149). Additionally, intracellular UA is pro-inflammatory by inducing NADPH-oxidases that lead to oxidative stress and cancer (151, 152). This again emphasizes the complex nature of these disorders in relation to cancer (**Table 1**).

Together, the lack of consensus in predisposition to cancer in DPPM patients points to the significant redundancy in the dNTP biosynthetic pathways. This should not be surprising due to the fact that dNTP synthesis is critical for organismal survival and, therefore, we have evolved to have multiple metabolic arms feeding into the same pathway. Understanding whether these patients

are predisposed or not to cancer will be incredibly important for the clinical management of these patients.

THERAPEUTIC MODULATION OF DEOXYRIBONUCLEOTIDE METABOLISM IN CANCER AND METABOLIC DISEASE

As described in this review, the balance of dNTPs must be tightly regulated in the cell. Many cancer types show alterations in dNTP levels, supporting their rapid proliferation. Likewise, defective mutations in anabolic and catabolic nucleotide enzymes, causing imbalances in the dNTP pools or in their precursors, are associated with different grades of disease severity in DPPM. Thus, it is not surprising that therapies for both cancer and DPPM focus on restoration of the normal balance of intracellular nucleotides.

Some of the first chemotherapeutic agents were cytotoxic nucleoside analogs and nucleobases (e.g., thiopurines and fluoropyrimidines) (153). These antimetabolites have a similar molecular structure to endogenous nucleotides and interfere with nucleotide metabolic pathways and DNA/RNA synthesis (154). Inhibitors of RNR were one of the first cancer therapies [reviewed in Ref. (53)] and are still used today. For instance, gemcitabine, a chemotherapeutic nucleoside analog, is used in pancreatic adenocarcinoma, but also in breast, bladder, and non-small cell lung cancer (155). Unfortunately, resistance to gemcitabine in common, often through an increase in nucleotide synthesis pathways or transport of nucleosides (156). Other successful chemotherapeutic regimens include methotrexate, which reduces substrates for purine and pyrimidine biosynthesis (157). Finally, specific inhibition of enzymes in the *de novo* pathway and/or in anapleurotic reactions (glucose and glutamine metabolism) has also been used as adjuvant therapies in cancer (154).

The spectrum of nucleotide therapies for DPPM is much broader in scope due to the high variability of deficiencies (3). Thus, deficiencies resulting in the overproduction of UA are treated with allopurinol, an inhibitor of xanthine oxidase (16). In other cases, patients can be treated with oral supplements of specific nucleotides they are lacking (16). What is clear is that cancer patients with DPPM cannot be treated with antimetabolites such as 5-fluoro-uracil due to severe side effects (19). This suggests that cancer patients, DPPM must remain above a certain threshold of nucleotide pools to remain healthy. Finally, no nucleotide therapies are currently used for MDs, such as diabetes or obesity. More studies will need to be performed to determine whether nucleotide metabolism plays a contributing role to these pathologies before these types of therapies can be tested.

CONCLUSION

For decades researchers and clinicians alike have recognized the importance of fine-tuned dNTP levels for cellular homeostasis, as shown by the number of anti-cancer therapies based on the abolishment of nucleotide synthesis. In addition, the broad range of pathologies associated with congenital defects in nucleotide metabolic enzymes further demonstrates the importance of healthy intracellular dNTP levels. However, the association between cancer and MD and whether nucleotide pools are interconnected in these pathologies remains unclear. Future work will need to focus on mechanistic and population-based studies to determine whether nucleotide pool imbalances in MD lead to changes in cancer predisposition and whether targeting these pathways for cancer therapy affects metabolic homeostasis and function in normal cells.

AUTHOR CONTRIBUTIONS

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