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·综 述·

尿苷对线粒体功能的影响

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摘 要：尿苷是生物体内必需的营养物之一，需将尿苷浓度维持在一定浓度水平才能维持胞内正常的生长代谢。近年来，有研究发现尿苷可通过多种机制缓解生物体炎症反应，并能参与胞内糖酵解等代谢途径，且可调节胞内糖基化、乙酰化等蛋白修饰作用。此外，其还能通过减轻胞内氧化应激、促进高能化合物合成等方式保护细胞免受缺氧性损伤。研究表明，这些保护作用与尿苷对线粒体功能的调节作用息息相关。因此，本文主要综述了尿苷及其代谢反应(物)对线粒体功能的研究进展。
关键词：尿苷；线粒体；线粒体 ATP 依赖性钾离子通道；嘧啶核苷酸池

Effect of uridine on mitochondrial function

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Abstract: Uridine is one of the essential nutrients in organisms. To maintain normal cell growth and intracellular metabolism, the uridine must be maintained at certain concentration. Recent studies have shown that uridine can reduce inflammatory response in organisms, participate in glycolysis, and regulate intracellular protein modification, such as glycosylation and acetylation. Furthermore, it can protect cells from hypoxic injury by reducing intracellular oxidative stress, promoting high-energy compounds synthesis. Previous studies have shown that the protective effects of uridine are closely related to its effect on mitochondria. This review summarizes the effect of uridine on mitochondrial function.
Keywords: uridine; mitochondria; mitochondrial ATP-dependent potassium channels; pyrimidine nucleotide pool

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尿苷是细胞内 RNA 与生物膜合成过程所必需的嘧啶核苷[1]，其在神经保护[2-4]、生化调节[5]、糖酵解[6]等多种生物过程中发挥重要的作用。

在胞内，尿苷主要通过嘧啶的从头合成途径和补救途径进行补充。在哺乳动物体内，尿苷的从头合成受到雷帕霉素靶蛋白(target of rapamycin, TOR)信号通路的严格调控[7]。此外，尿苷在血液中的稳态受进食调控，与体温密切相关，且其在生理功能方面可能与瘦素有一定的协同作用[8]。

尿苷可调节尿苷代谢中的酶和中间产物，进而影响胞内葡萄糖稳态、脂质代谢和氨基酸代谢等[9]。此外，近期有研究表明，尿苷可以保护阿兹海默症患者的成纤维细胞和正常的人类神经祖细胞，使其免受线粒体呼吸链复合物IV抑制剂叠氮化物的毒性作用[10-11]。据报道，氰化钾(potassium cyanide, KCN)对神经母细胞瘤 SHSY5Y 具有损伤作用，会使其尿苷胞苷激酶 2 的 mRNA 水平和 β III-tubulin 等蛋白水平发生改变，而添加 200 μmol/L 尿苷可以在一定程度上缓解 KCN 的损伤作用[12]。尿苷还具有抗氧化作用，在新生大鼠高氧性脑损伤模型中，添加尿苷可防止高氧诱导的活性氧(reactive oxygen species, ROS)浓度升高和谷胱甘肽过氧化物酶减少[13]，通过清除 ROS 来维持线粒体功能[14]。尿苷也可抑制线粒体凋亡，从而维持氧化磷酸化等线粒体功能。

根据文献初步推测，这些积极作用可能与其对线粒体功能的调控作用有关。因此，本综述深入探究了尿苷对线粒体功能的影响作用，以期指导基于哺乳动物细胞培养的生物药生产工艺的开发与优化。

1 尿苷对动物细胞培养工艺的影响

根据前期研究结果，在基于重组 CHO 细胞等哺乳动物细胞培养工艺的生物药生产中，尿苷对细胞生长、代谢以及目的产物的表达具有积极作用。

具体而言，在细胞生长方面，添加尿苷可获得更高的细胞密度(viable cell density, VCD)，并能改善细胞活率(viability, VIA)维持(图 1A)。细胞代谢方面，尿苷可促进细胞的葡萄糖(glucose, Gluc)代谢和缓解乳酸(lactate, Lac)积累问题(图 1B)。此外，其还能够在不影响目的产物蛋白质量的前提下提高产物蛋白的产量(titer)和单位细胞蛋白产率(peak viable cell density, Q_p) (表 1)。

2 尿苷通过激活线粒体 ATP 依赖性钾通道调节生理反应(图 2)

线粒体 ATP 依赖性钾通道(mitochondrial ATP-dependent potassium channels, mitoK_{ATP})其研究可追溯至 1991 年，首次发现于大鼠肝细胞线粒体内膜上，为一种非电压依赖性配体门控通道[15]。迄今为止，mitoK_{ATP} 的结构尚未十分明确，仅能确定其与现已研究得较为清楚的细胞膜 ATP 依赖性钾离子通道的结构较为相似[16]。有文献表明，mitoK_{ATP} 中可能包含线粒体呼吸链复合物II[17]。

mitoK_{ATP} 与细胞生长息息相关，其功能可能具有两面性。一方面，mitoK_{ATP} 的开放会导致线粒体膜电位(mitochondrial membrane potential, MMP)崩溃，使线粒体内产生 ROS。另一方面，这种诱导线粒体膜电位崩溃的 mitoK_{ATP} 开放结构却有利于多类细胞的增殖和存活[18-19]。也有

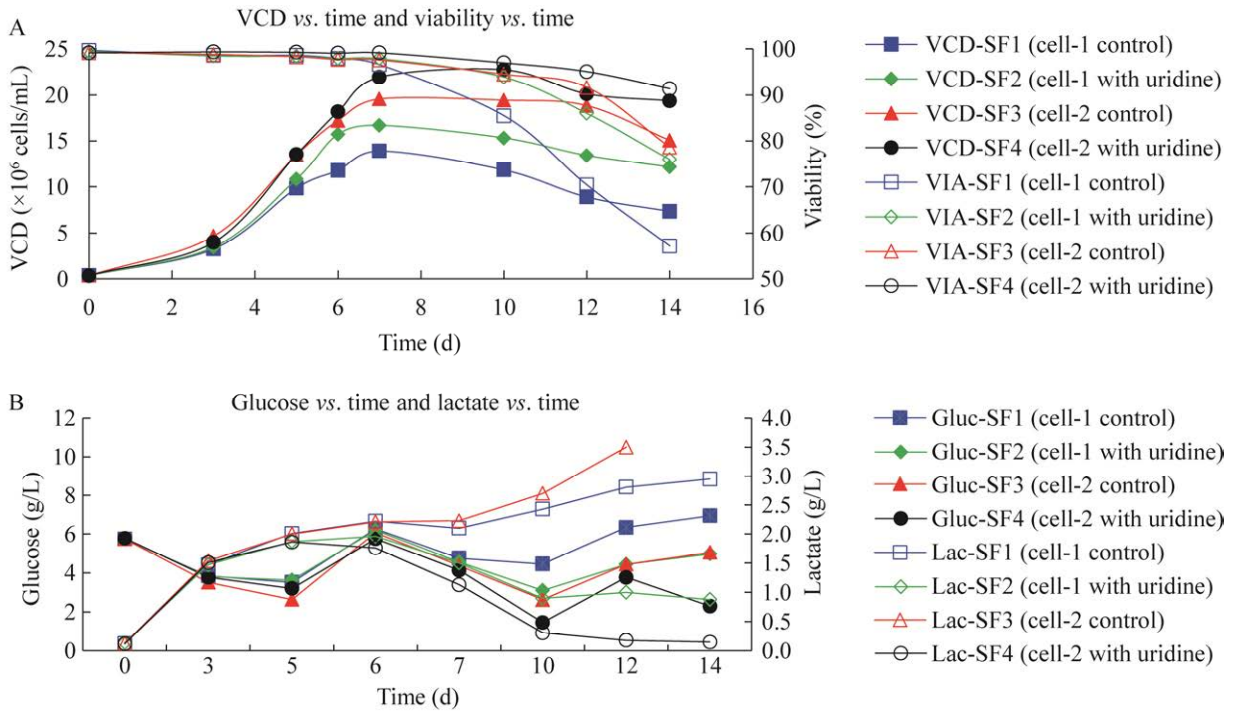

图 1　重组 CHO 细胞(cell-1 和 cell-2)生长代谢图　SF1 和 SF3：分别为 cell-1 和 cell-2 的对照条件；SF2 和 SF4：分别为 cell-1 和 cell-2 添加尿苷的条件. A：重组 CHO 细胞在培养过程中的细胞密度和细胞活率. B：重组 CHO 细胞在培养过程中的葡萄糖浓度和乳酸浓度

Figure 1　Diagram of growth and metabolism of recombinant CHO cells (cell-1 and cell-2). SF1 and SF3: Control conditions for cell-1 and cell-2; SF2 and SF4: Conditions for adding uridine to cell-1 and cell-2. A: Cell density and cell viability of recombinant CHO cells during culture. B: Glucose concentration and lactate concentration of recombinant CHO cells during culture.

表 1　重组 CHO 细胞收获当天的蛋白产量、产率和部分蛋白质量

Table 1　Nominalized titer, nominalized Qp and partial protein quality of recombinant CHO cells on the day of harvest

No.	Comment	Nominalized Q_p	Nominalized titer	N-glycan results (%)				
				G0	G0F	G1F	G2F	Man5
SF1	Cell-1 control	1.00	1.00	1.6	78.0	ND	0.4	1.1
SF2	Cell-1 with uridine	1.67	2.12	2.4	78.5	0.2	0.4	1.1
SF3	Cell-2 control	1.00	1.00	0.9	71.6	ND	0.7	0.7
SF4	Cell-2 with uridine	1.62	1.79	3.8	64.2	ND	0.9	0.9

研究表明，激活 mitoK$_{ATP}$ 通道可防止线粒体功能障碍[20]。

胞内一些物质对 mitoK$_{ATP}$ 活性具有调控作用，如尿苷二磷酸(uridine diphosphate, UDP)。与细胞膜 ATP 依赖性钾通道相比，激活 mitoK$_{ATP}$ 所需的 UDP 浓度阈值更低[21-22]。通常，UDP 无法直接通过细胞膜进入胞内，故常以 UDP 的前体尿苷作为前体药物来调控 mitoK$_{ATP}$ 活性[23]，其对 mitoK$_{ATP}$ 的激活作用强于常用的 mitoK$_{ATP}$ 激动剂二氮嗪[24]。例如，Mankovskaya 等[25]研

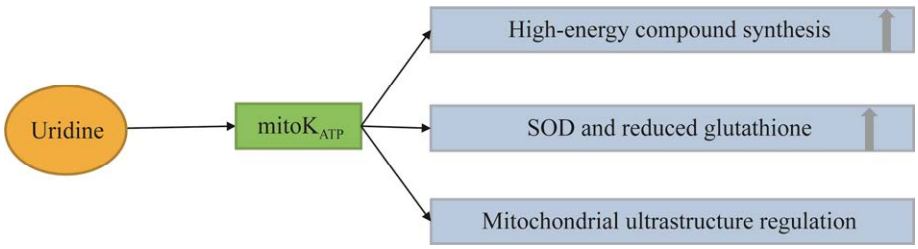

图 2　尿苷通过激活线粒体 ATP 依赖性钾通道调节生理反应的示意图

Figure 2　Diagram of regulating physiological responses by uridine through activation of mitochondrial ATP-dependent potassium channels.

究表明尿苷可以通过激活 mitoK$_{ATP}$ 提高大鼠对缺氧环境的抵抗力。Bul'on 和 Krylova 等[26]通过研究发现了类似现象，给缺血/再灌注损伤模型大鼠注射尿苷，再检测腺苷三磷酸(adenosine triphosphate, ATP)、肌酸磷酸(phosphocreatine, PCr)、超氧化物歧化酶(superoxide dismutase, SOD)和还原性谷胱甘肽的含量。结果表明，尿苷可通过激活 mitoK$_{ATP}$ 维持 ATP、PCr 和还原性谷胱甘肽的含量，并阻止 SOD 减少。Krylova 等[27]研究了尿苷对急性缺血模型大鼠的影响，同样发现尿苷可通过提高胞内 UDP 含量来激活 mitoK$_{ATP}$，进而阻止急性缺血大鼠心肌中的高能化合物耗竭和提高其抗氧化能力。据此，Mironova 等[28]提出，可利用尿苷对线粒体功能的调节作用来治疗新型冠状病毒感染及其并发症。

进一步深入分析可知，尿苷的上述作用是通过激活 mitoK$_{ATP}$ 调控线粒体系统功能实现的[29]。通常，在急性缺氧条件下线粒体的超微结构会发生明显变化，具体表现为：线粒体基质出现不同程度的肿胀，部分或完全空泡化；嵴排列紊乱；线粒体膜受到破坏；有时甚至形成特殊的紧凑光学结构——微线粒体[24]。Rozova 等[30]以急性缺氧大鼠模型为研究对象，通过电子显微镜观察线粒体结构与数目，发现在缺氧前注射尿苷可激活 mitoK$_{ATP}$，进而明显降低大鼠肺细胞中结构紊乱的线粒体数量，并显著减少细胞器过度肿胀。不过，其并未显著缓解由缺氧所致的线粒体总数增加的问题。Mironova 等[24]研究表明，尿苷可通过激活 mitoK$_{ATP}$ 明显改善大鼠心肌细胞中线粒体的能量导向，即增强高能化合物合成反应[24]。此外，尿苷激活 mitoK$_{ATP}$ 后可加快线粒体分裂，进而形成微线粒体结构。

除增强机体对缺氧环境的抗性外，尿苷还可通过激活 mitoK$_{ATP}$ 来缓解由内毒素引起的雄性 BALB/c 小鼠 NF-κB 活化和细胞因子分泌所引发的炎症[31]。

3　尿苷通过补充嘧啶核苷酸池维持线粒体功能(图 3)

细胞凋亡或一些化学药物作用均可能损伤线粒体，从而导致线粒体 DNA (mitochondrial DNA, mtDNA)释放[32]和损伤消耗。尿苷可有效缓解此类线粒体损伤，且具有较高的安全性[33-35]，故其常被应用于预防和治疗由扎西他滨(zalcitabine, DDC)等核苷类似物逆转录酶抑制剂(nucleoside analogues reverse transcriptase inhibitors, NRTIs)引起的线粒体毒性和 mtDNA 消耗[35-37]，进而消除抑制剂对细胞增殖的不利影响[36]。例如，将 100 mg/mL 丙酮酸和 50 mg/mL 尿苷联合使用，可以使 mtDNA 缺陷的 U937-rho

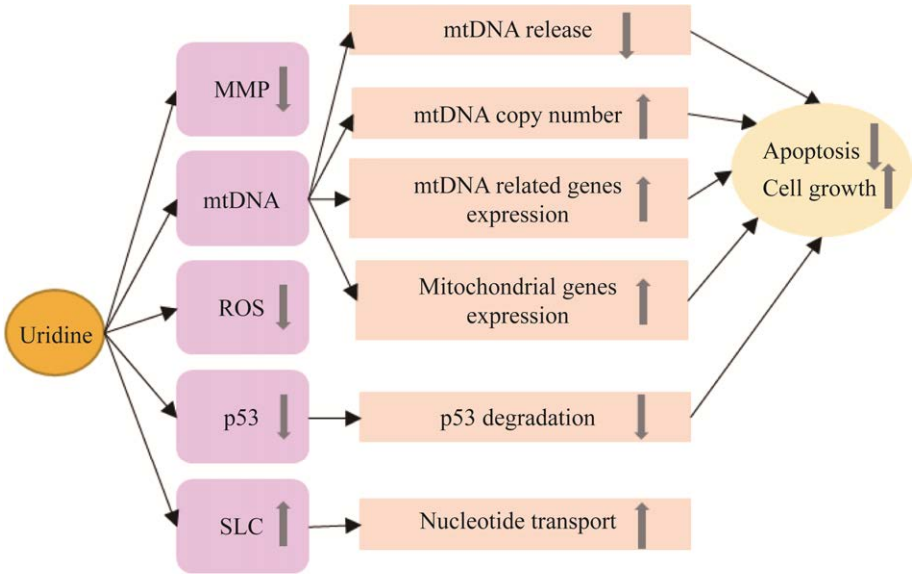

图 3　尿苷通过补充嘧啶核苷酸池维持线粒体功能的示意图

Figure 3　Diagram of maintaining mitochondrial function by uridine through replenishing the pyrimidine nucleotide pool.

细胞维持正常生长[38]。Lebrecht 等发现，接受齐多夫定(zidovudine, AZT)治疗的小鼠的细胞器中 mtDNA 拷贝数减少，且细胞色素 C 氧化酶活性下降，补充尿苷可以有效缓解这些问题[39-40]。当利什曼原虫细胞的 mtDNA 耗竭后，可通过补充外源性尿苷和丙酮酸使其存活和恢复增殖能力[41]。在临床试验中，无下路尿症患者需服用具有线粒体毒性的抗生素，这会降低体内 T 细胞的增殖能力，采用尿苷和丙酮酸的联用的策略可以保护 T 细胞免受这种线粒体毒性[42]。Iglesia 等认为尿苷还可能对携带 mtDNA 病理突变的孕期女性具有一定的保护作用[43]。

尿苷之所以对细胞有上述保护作用，主要原因在于线粒体毒性和 mtDNA 消耗通常与嘧啶缺乏相关[44-45]。嘧啶是 DNA、RNA、糖蛋白和磷脂生物合成的必需物质，在胞内一般通过从头嘧啶合成和嘧啶补救途径补充嘧啶核苷酸池。缺乏嘧啶会诱发 mtDNA 释放[32]、耗竭[46]以及 p53 激活，从而导致线粒体功能障碍，最终抑制细胞增殖或使细胞发生凋亡[47]。Liu 等[34]证明，尿苷可以调节嘧啶核苷酸代谢过程相关的基因表达，例如：尿苷可以提高人骨髓间充质干细胞中线粒体基因和 mtDNA 相关基因的表达水平。此外，其还可间接调控嘧啶代谢过程。

3.1　尿苷对二氢乳清酸脱氢酶的影响

在快速增殖的细胞中，嘧啶的来源以从头嘧啶合成为主[48]。当从头嘧啶合成受到抑制时，可能使胞内严重缺乏嘧啶。在嘧啶从头合成途径中，二氢乳清酸脱氢酶(dihydroorotate dehydrogenase, DHODH)是其重要的限制酶。方静娴等[49]研究表明，当 DHODH 表达受到抑制时，mtDNA 减少近 30%，且细胞发生 G_2/M 周期阻滞。口服尿苷可改变小鼠体内包括 DHODH 在内的尿苷代谢相关基因的表达水平[50]。不过，体外实验中尿苷对 DHODH 并无明显影响[51]。

由于 DHODH 是嘧啶从头合成中唯一位于线粒体上的限速酶，故其也与电子传递链密切相关[48]。因此，当呼吸链功能出现障碍时，尤

其是线粒体呼吸链复合物III受到抑制时，DHODH 也会受到相应的抑制，进而影响嘧啶从头合成[52-53]，最终导致尿苷不足[54]。据此，在一定程度上 DHODH 的活性取决于氧化磷酸化功能。Khutornenko 等[55]研究发现，人类结肠癌细胞线粒体呼吸链复合物III受到抑制后会发生凋亡，在此条件下添加尿苷或者乳清酸盐则可防止凋亡，这间接证明 DHODH 与线粒体呼吸链相关。

同时，DHODH 抑制剂也对 p53[56-57]、MMP[58]、ROS[49,54,59]、线粒体脂质过氧化[60]和其他一般线粒体代谢参数都有重要影响，而外源性尿苷则可缓解这些影响。例如，DHODH 抑制剂 MEDS433 可通过降低 DHODH 活性抑制单纯性疱疹病毒(herpes simplex virus, HSV)在细胞内的复制，添加尿苷可以逆转 MEDS433 的作用[61]。Boukalova 等[54]通过 CRISPR/Cas9 基因编辑技术敲除小鼠乳腺癌细胞和小鼠黑色素瘤细胞中的 DHODH 基因进行研究发现，DHODH 缺陷会使细胞增殖受到抑制，而补充尿苷则可使细胞增殖恢复。在心肌细胞[62]和上皮癌细胞[63]培养中，可通过补充尿苷缓解 p53 介导的细胞凋亡。在不添加尿苷的条件下，DHODH 抑制剂 AG-636 会使 UMP 减少 80%以上，从而对细胞代谢和生长产生抑制作用，补充 100 μmol/L 尿苷能缓解抑制作用和使 DHODH 下游的代谢水平得到恢复[48]。此外，尿苷通过补充嘧啶池改变线粒体磷脂的组成(特别是乙醚磷脂)，进而减少由 DHODH 抑制引起的应激反应[64]。

3.2 尿苷对 p53 的影响

抑癌基因 *p53* 是维持线粒体基础功能的重要基因，其所编码的 p53 蛋白可调控呼吸链功能至关重要的几个核编码蛋白和 mtDNA 拷贝数[65]，其还与 mtDNA 损伤[65-69]和线粒体外膜通透性[70]息息相关。

在内皮细胞中，缺失 p53 会显著减少线粒体重塑[71]。在卵巢瘤细胞中，p53 通过 p62 的泛素结合域(ubiquitin-associated domain, UBA domain)定位于线粒体上，使线粒体内 p53 积累，从而弱化线粒体 RNA 聚合酶 POLRMT 功能，最终下调 mtDNA 转录水平[72-73]。研究表明，嘧啶核苷酸库缺乏可强烈诱导 *p53* 相关反应[63]，且 p53 的稳定性与尿苷相关。在缺乏尿苷的条件下，p53 降解作用变弱，p53 蛋白增多，而尿苷能以剂量依赖性的方式降低 p53、Bax、caspase 9 和 caspase 3 等蛋白水平[74]。Pritchard 等[75]发现，在肠上皮细胞培养中添加尿苷可抑制 p53 依赖性的细胞死亡。Zhang 等[74]的研究也得出了相似结论，利用雷公藤红素(celastrol)激活人早幼粒白血病细胞的 p53 途径会诱导细胞凋亡，而添加外源性尿苷可以抑制凋亡。在 ARN8 细胞培养中，添加尿苷可以完全抑制长寿因子抑制剂 tenovin1 和 tenovin33 对 *p53* 转录的诱导作用，并降低 p53 蛋白水平[56]。

3.3 尿苷溶质载体蛋白的影响

除了上述对线粒体基因、DHODH 和 *p53* 的调节作用以外，尿苷还可通过提高载体蛋白表达水平来改善嘧啶核苷酸的生物利用度。通过膳食补充一磷酸尿苷(uridine monophosphate, UMP)或尿苷有助于提高乳猪十二指肠和小鼠肝脏中溶质载体家族 28 成员 1 (solute carrier family 28 member 1, SLC28A1)和 SLC29A1 的 mRNA 表达水平，从而促进肠道发育和核苷酸转运[50,76]。也有研究表明添加尿苷可以提高 SLC25 的表达水平，而 SLC25 在维持线粒体生物发生中起到重要作用[77-78]。在小鼠胚胎干细胞中，SLC25A36 缺乏与 mtDNA 消耗、MMP 降低和线粒体功能障碍相关，Jasper 等证明口服尿苷可有效治疗 SLC25A36 缺乏引起的相关症状[58]。

3.4 嘧啶补救途径对尿苷的影响

尿苷通过人平衡型核苷转运蛋白1或2 (human equilibrative nucleoside transporter, hENT1/2)或者人富集型核苷转运蛋白(human concentrative nucleoside transporter, hCNT)进入细胞，进而通过补救途径补充胞内嘧啶核苷酸池。不过，当胞内嘧啶的从头合成和补救途径同时受到抑制时，便无法再添加尿苷补充嘧啶核苷池。例如，嘧啶从头合成途径的抑制剂 MEDS433 可使多种急性髓性白血病(acute myeloid leukemia, AML)细胞发生凋亡，添加超出生理剂量的尿苷则可有效阻止凋亡。单独以 hENT1/2 的抑制剂双嘧达莫(dipyridamole)处理 AML 细胞并不能产生任何影响，但以 MEDS433 和双嘧达莫同时处理 AML 细胞时，则会强烈促进细胞凋亡[47]。在被 SARS-CoV-2 感染的人肺腺癌细胞培养中，Calistri 等[65]发现添加尿苷可以逆转 0.25 μmol/L MEDS433 对 SARS-CoV-2 体外复制过程的抑制作用。但是，若将 MEDS433 与双嘧达莫联合使用，则添加尿苷并不能逆转二者对 SARS-CoV-2 复制的抑制作用。

4 尿苷代谢产物对线粒体的调节(图 4)

细胞内尿苷有多种代谢产物，主要包括 UDP、UMP、β-丙氨酸、乙酰 CoA 等。UDP 和 UMP 对线粒体的影响与尿苷的作用有一定的相似性[31,76,79-80]，此处不再赘述。

4.1 β-丙氨酸

β-丙氨酸属于典型的“运动促进剂”[81]，但 β-丙氨酸对代谢、运输等胞内反应的作用机制相关研究较少，且其对线粒体相关功能的影响作用也尚未有统一的结论，故其对线粒体功能的影响有待进一步探索。

部分研究表明，β-丙氨酸对线粒体具有积极作用。例如，β-丙氨酸可保护大鼠肝细胞免受缺氧性损伤[82]。氧化物酶体增殖物激活受体 γ 共激活因子 α (peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α)是线粒体生物合成的主要调节因子，Schnuck 等在心肌细胞 C2C12 培养中发现添加 800 μmol/L β-丙氨酸显著提高 PGC-1α 的 RNA 水平和线粒体转录因子 A

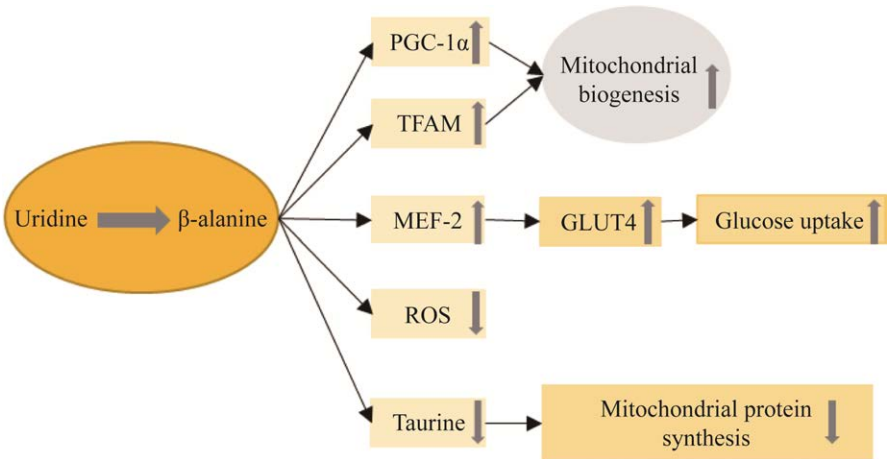

图 4 β-丙氨酸对线粒体调节的示意图

Figure 4 Diagram of mitochondrial function regulated by β-alanine.

(mitochondrial transcription factor A, TFAM)的表达水平，且能通过增强肌细胞增强因子 2 (myocyte enhancer factor-2, MEF-2)来提高其下游葡萄糖转运蛋白 4 (glucose transporter 4, GLUT4)的含量[83]。这些结果表明，β-丙氨酸可能具有促进线粒体生物发生和增强细胞对葡萄糖的摄取能力的作用。Wang 等[84]发现，虽然β-丙氨酸本身并不具有清除氧自由基的作用，但向贻贝注射 β-丙氨酸可以提高贻贝组织内自由基的清除能力。此外，β-丙氨酸还可延迟胞内乳酸的积累。但是，β-丙氨酸和牛磺酸(taurine)具有相同的转运受体，故二者在摄取时会相互竞争转运受体[81,85]。不过，细胞质和线粒体的牛磺酸水平并非直接耦合。因此，虽然外源性β-丙氨酸会使细胞质内牛磺酸水平下降，但其对线粒体牛磺酸水平影响并不明显[86]。尽管如此，β-丙氨酸仍会干扰受牛磺酸调节的线粒体蛋白质的合成[86]。Vaughan 等[87]向恶性乳腺上皮细胞中添加 100 μmol/L β-丙氨酸，发现其可明显抑制糖酵解和氧化代谢，降低线粒体含量和抑制促线粒体合成相关基因的表达。

4.2 乙酰 CoA

尿苷代谢的下游产物乙酰 CoA 也是三羧酸循环(tricarboxylic acid cycle, TCA)的重要中间产物。研究表明，添加尿苷可以提高细胞内乙酰 CoA 的浓度，从而促进 TCA 循环[31]。而且，尿苷还可调节肝脏蛋白、组蛋白和其他蛋白质的乙酰化作用[88-89]。由于乙酰 CoA 是蛋白乙酰化作用的共同底物[88]，故这些作用可能也与尿苷分解产生乙酰 CoA 相关。

除去上述尿苷对 mitoK$_{ATP}$、嘧啶核苷酸池以及其代谢产物对线粒体的影响以外，尿苷还可以通过调节葡萄糖代谢和脂肪代谢，间接对 TCA 循环产生影响。TCA 循环是需氧生物体内普遍存在的代谢途径，真核细胞的 TCA 循环发生于线粒体中。脂肪和碳水化合物分解是 TCA 循环的前提[90]，葡萄糖通过糖酵解产生的丙酮酸和脂肪分解产生脂肪酸，这 2 个产物是 TCA 循环促进物乙酰 CoA 的底物。因此，糖酵解和脂肪酸分解对 TCA 循环具有重要意义。据研究，尿苷对脂肪和碳水化合物分解具有重要的影响作用(图 5)。

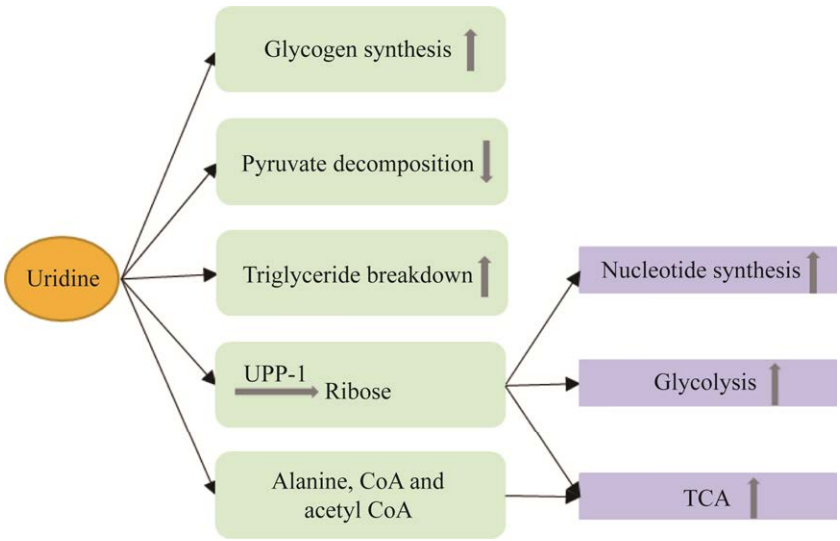

图 5 尿苷调节葡萄糖和脂肪代谢的示意图

Figure 5 Diagram of regulating glucose and fat metabolism by uridine.

联合使用尿苷和肌苷可以调节骨骼肌的葡萄糖代谢[5]。当葡萄糖供应充足时，UTP 前体尿苷可以激活糖原合成途径和阻止丙酮酸分解[27]。当葡萄糖供应受限时，尿苷则可以作为葡萄糖的替代物。Jourdain 等[91]的研究表明，在葡萄糖供应受限的条件下细胞会从尿苷或 RNA 中回收核糖以支持糖酵解。Ward 等[92]利用营养学分析方法揭示，在营养缺陷的胰腺导管癌细胞中，尿苷通过尿苷磷酸酶 1 (uridine phosphorylase, UPP-1)分解生成核糖，后者进入中心碳循环以促进糖酵解、TCA 循环和核苷酸合成，从而维持肿瘤生长。此外，敲除 UPP-1 会影响肿瘤生长。这两项研究表明，尿苷或 RNA 也可以作为潜在的能量存储载体。

除了通过中心碳代谢途径促进 TCA 循环以外，尿苷还可以通过促进丙氨酸、CoA 和乙酰 CoA 的形成来激活 TCA 循环[31]。

脂肪组织和肝脏组织是内源性尿苷的重要供应源[93]。在小鼠脂肪细胞中，可通过过量表达 X-框结合蛋白 1 (X-box binding protein 1, XBP1)激活氨甲酰磷酸合成酶 2-天冬酰胺转氨甲酸酯酶-二羟乳清酶(carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase, CAD)，从而促进嘧啶生物合成[94]。Liu 等[9]发现，对于高脂饮食喂养的小鼠，尿苷可减少肝脂质积累，且在一天中的不同时间补充尿苷会使 10 种不同的脂肪酸的含量发生波动[42]。尿苷的合成作用可以促进甘油三酯分解，且前者合成越活跃，后者分解速率越快[8]。因此，尿苷在脂肪酸组成和脂质代谢中起到重要作用[76,95]。不过，Urasaki 等[96]发现，长期喂养尿苷也会诱导小鼠全身葡萄糖耐受不良，并造成严重的肝脏脂质积累。因此，尿苷对糖酵解和脂肪分解的作用可能具有两面性，尚待进一步研究。

5 总结

尿苷是参与 RNA、生物膜和糖原合成的重要核苷[8]，在细胞生长和代谢的过程中发挥着重要的作用。尿苷通过激活 mitoK$_{ATP}$ 以促进 PCr 的合成、提高细胞的抗氧化能力和调节线粒体系统功能。同时，尿苷可以补充嘧啶核苷酸池，以缓解由 mtDNA 损伤引起的线粒体损伤，抑制细胞凋亡。此外，尿苷的多种代谢产物(例如：UDP、β-丙氨酸、乙酰 CoA 等)也在维持线粒体功能方面有积极作用。因此，在细胞培养工艺开发的过程中添加一定浓度的尿苷可以使细胞更好地维持生长、代谢和多种生理功能。

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