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·综述·

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# tRNA 核苷修饰与细胞胁迫应答

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**摘要** 细胞的生长和功能发挥需要特定的内部条件。当外界条件发生变化时,细胞要想保持这种特定的内部环境,需要许多过程的参与,其中最重要的一个部分是 RNA 代谢调节,其通常涉及一般翻译水平的下降和应激反应,以有利基因翻译的增加。tRNA 是翻译机制的一个基本组成部分,在蛋白质合成过程中,它将氨基酸传递给核糖体。tRNA 的显著特征之一是高度修饰,这些修饰有大量用途,包括确保翻译的准确性和高效性、维持 tRNA 折叠或稳定性等。细胞在逆境胁迫条件下,tRNA 修饰水平会发生显著变化,并通过不同的途径影响细胞的翻译。本文阐述了 tRNA 核苷修饰与细胞胁迫之间的相互关系,描述了 tRNA 修饰响应胁迫应答的可能机制。

**关键词** 代谢调节; 翻译; 转运 RNA; 核苷修饰; 胁迫应答
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# tRNA Nucleoside Modification and Cell Stress Responses

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**Abstract** Cellular organisms require specific internal conditions for optimal growth and function. Upon variable environments, many strategies have involved to maintain these internal conditions. One of the most important response is the metabolic regulation of RNAs, which usually involves a decrease in the level of general translation and an increase of stress-specific proteins. tRNAs are the fundamental components of the translation machinery as they deliver amino acids to the ribosomes during protein synthesis. Prevalent modifications are one of the characteristics of tRNAs. These modifications have many purposes, including ensuring translation fidelity and efficiency, and maintaining tRNA folding or stability. When cells are subject to stress, tRNA modification levels will change significantly, and affect cell translation through different pathways. In this paper, we review the relationship between tRNA nucleoside modification and cellular stress, and describe the possible mechanisms of tRNA modification in response to cellular stresses.

**Key words** metabolic regulation; translation; transfer RNA (tRNA); nucleoside modification; stress response

## 1 tRNA 核苷修饰

转运 RNA(transfer RNA,tRNA)是主要负责将 mRNA 解码成相应的多肽序列的衔接分子,其基本构成单元只有 4 种核糖核酸(A、U、C 和 G)。这 4 种核糖核酸可被不同的酶修饰,形成不同的化学结构。这些修饰多种多样,从简单的核糖甲基化到嘌呤或嘧啶环不同位置的复杂的化学修饰[1]。RNA

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修饰数据库(http://mods.rna.albany.edu/mods/modifications/)显示,目前已经发现的 tRNA 核苷修饰有 100 多种,占所有 RNA 修饰核苷种类的 90%以上。tRNA 核苷修饰在古细菌、细菌和真核生物中普遍存在[2]。其中,一些特定位点的核苷修饰(例如 Ψ、$t^6A$、$m^1G$、$m^7G$、Cm、Um 和 Gm)是非常保守的,表明他们有着共同的进化起源。但在古细菌、细菌以及真核生物中,也存在着各自特定的修饰,这些修饰的种类以及位置在这 3 大物种中有着显著的差异。

一般来说,tRNA 核苷修饰能够加强核糖体结合的亲和力、减少解码的误读、调节移码突变,所有这些修饰都将影响翻译的效率和精确性[3-6]。tRNA 结构上某些特定位点的修饰有利于 tRNA 的正确折叠,并对稳定其三级结构有一定帮助[7,8]。由于 tRNA 修饰在结构和功能上的作用,缺乏 1 个或多个 tRNA 修饰,将会产生易于出错的翻译系统。在某些情况下,这将影响生物体的生长发育。例如,反密码子环上第 37 位 $m^1G$ 的缺失,会影响拟南芥的生长发育,造成生育期延迟和结实率低等[9];$m^5C$ 的缺失使拟南芥根长受到抑制[10]。通常,细胞利用自身调节能处理各种错误的翻译系统。因此,在正常情况下,大多数修饰的缺失对生长的影响极小。最近大量的研究表明,这些修饰的作用是在特定条件下被显示的,如细菌与寄主之间相互作用、胁迫或其他蛋白质的丢失等[11]。

## 2 tRNA 修饰在胁迫应答中的调节作用

许多 tRNA 修饰并不是生物体生存必不可少的,这些"不必要的功能"在大量生物学特性中很常见。例如,大量 DNA 和蛋白质的修饰是不必要的,而不必要的蛋白质修饰,往往在细胞应激反应中发挥重要作用。同样,tRNA 的化学修饰也可以作为细胞的传感器,使细胞在逆境中能更好的生存[12](Table 1)。

大肠杆菌 tRNA 第 8 位 4-硫代尿苷($s^4U$)是由 NuvA 和 NuvC 两种酶串联催化形成的。*nuvA* 缺失突变体比野生型更容易被宽频的近紫外线杀死,说明 $s^4U$ 可能有助于细胞抗紫外胁迫[28]。某些 tRNA 摆动碱基 $mcm^5U$ 的出现,对细胞在遭受烷基化损伤后的生存至关重要[33],这是 tRNA 摆动碱基的修饰状态与细胞应激反应之间关系的 1 个例子。

在酵母中,tRNA 反密码子环摆动碱基 $mcm^5S^2U34$ 的修饰依赖于延伸蛋白(elongator protein, ELP)和泛素相关修饰因子(ubiquitin-related modifier,1 URM1)的活性,转录延伸复合体(Elp1-Elp6)和 Kti11-13 以及 Trm9 共同负责 tRNA-$mcm^5$ 的形成[47,48];而 URM1 催化 $mcm^5$ 进一步硫醇化形成 $mcm^5s^2U$[30]。2013 年,Fernández-Vázquez 等通过研究证明,转录延伸复合体的 Elp3 亚基对裂殖酵母的抗逆性非常重要,*elp*3 缺失突变体对 $H_2O_2$ 和高温等非常敏感,并证明这种逆境表型是由于 tRNA 修饰的缺失所致[35]。Vilahermosa 和 Fleck 在粟酒裂殖酵母中也发现,*elp*3 缺失突变体对许多细胞毒性药物(甲磺酸甲酯、噻苯咪唑以及雷帕霉素等)敏感,并且在低温条件下(16 ℃)表现出生长缺陷,而在高温条件下(37 ℃)基本不能生长[36]。*urm*1 缺失突变体表现出不同的表型,包括增加对氧胁迫的敏感性,对营养传感的缺陷和侵入性生长等。其中,许多都与 tRNA 修饰缺失有关[30, 42, 49]。研究发现,*urm*1 缺失突变体的翻译受损,从而增加了 Hsf1 介导的热休克反应的活性。同时,也发现温度升高时,野生型细胞的 tRNA 硫醇化水平降低[43]。此外,tRNA 硫醇化的缺失,在一定条件下是有利的,表现出对内质网应激反应的抗性[43]。

酵母特定 tRNA 的修饰水平降低,可能会导致其对 ROS、DNA 损伤试剂以及其他导致蛋白质翻译错误的试剂敏感。例如,*trm*4△细胞很容易被 $H_2O_2$ 杀死[15];*trm*9△细胞对促进 DNA 双链断裂和 S 时期损伤的试剂敏感[33, 34]。Trm140 能催化多种 tRNA 上 $m^3C32$ 的甲基化形成,酿酒酵母 *trm*140 缺失突变体细胞对烷化剂甲基甲磺酸(methyl methanesulfonate, MMS)和乙基甲磺酸(ethyl methanesulfonate, EMS)的敏感性显著增加[13]。在铜绿假单胞菌中,TrmJ 能够催化 tRNA 第 32 位上 Cm/Um/Am 的形成,缺失 TrmJ 表现出对 $H_2O_2$ 敏感[24]。tRNA-$m^5C$ 修饰是一种常见的 tRNA 甲基化修饰,在不同的物种中分别由几种不同的酶催化(Table 1),是逆境响应中调节细胞生存所必须的[17]。果蝇中,负责 $m^5C$ 修饰的酶 DNMT2 缺失后,连续在 29 ℃(比正常温度高 4 ℃)条件下培养时,突变体平均寿命减少,对氧胁迫更敏感[18]

为了确定特定 tRNA 修饰在毒物响应过程中的作用,Chan 等人对 tRNA 甲基转移酶基因,以及其他类型的 tRNA 修饰酶基因的缺失突变体进行了细胞毒性表型分析[14]。结果显示,与野生型相比,*trm*4($m^5C$)和 *trm*7(Cm)缺失突变体对 $H_2O_2$ 非常敏感;*trm*1($m_2^2G$)、*trm*4($m^5C$)、*trm*9($mcm^5U/mcm^5s^2U$)、*trm*44(Um)和 *mod*5($t^6A$)缺失突变体对 MMS 敏感;

**Table 1　tRNA modifications related to cell stress response**

| Modifications | Organisms[a)] | Modifying enzymes | Phenotypes[b)] | References |
|---|---|---|---|---|
| $m^3C$ | Yeast | Trm140 | Mutants were sensitive to alkylating agents | [13] |
| $m^5C$ | Yeast | Trm4 | Mutants were sensitive to MMS, $H_2O_2$, $NaAsO_2$, NaOCl | [14, 15] |
| | *H. sapiens* | Nsun2 | Mutants were sensitive to 5-FU, UV and oxidative stress | [16, 17] |
| | Mouse | Nsun2 | Mutants were sensitive to UV and oxidative stress | [17] |
| | *Drosophila* | DNMT2 | Mutants were sensitive to high temperature and oxidative stress | [18] |
| | *A. thaliana* | AtTrm4B | Mutants were sensitive to oxidative stress | [10] |
| | *E. histolytica* | Ehmeth | Ehmeth confer resistance to nitrosative stress | [19] |
| $m^1A$ | Rice<br>*A. thaliana* | Trm61/Trm6 | The level of $m^1A$ was decreased dramatically under cold or salt stress | [20] |
| $m^7G$ | *T. thermophilus* | TRMB | Mutants were sensitive to high temperature | [21] |
| | *Yeast* | TRM8/TRM82 | Mutants were sensitive to high temperature | [22] |
| | Rice<br>*A. thaliana* | | Level of $m^7G$ was decreased dramatically under cold or salt stress | [20] |
| Am | Rice<br>*A. thaliana* | OsTrm13<br>AtTrm13 | Mutants were sensitive to salt and ABA | [20, 23] |
| | *P. aeruginosa* | TrmJ | Mutants were sensitive to peroxides | [24] |
| Cm | Yeast | Trm7 | Mutants were sensitive to peroxides | [14] |
| | Rice<br>*A. thaliana* | OsTrm13 | Level of Cm was decreased dramatically under cold, drought, salt or ABA stress | [20, 23] |
| | *P. aeruginosa* | TrmJ | Mutants were sensitive to peroxides | [24] |
| Um | Yeast | TRM44 | Mutants were sensitive to MMS, $NaAsO_2$ | [14] |
| | *P. aeruginosa* | TrmJ | Mutants were sensitive to peroxides | [24] |
| $m_2^2G$ | Yeast | Trm1 | Mutants were sensitive to MMS, $NaAsO_2$ and high temperature | [14, 22] |
| | *H. sapiens* | | Mutants were sensitive to oxidative stress | [25] |
| $t^6A$ | Yeast | MOD5 | Mutants were sensitive to MMS | [14] |
| | *H. sapiens* | YRDC, OSGEPL1 | Mutants were sensitive to intracellular $CO_2$ | [26] |
| $i^6A$ | *H. sapiens* | TRIT1 | Mutants were sensitive to ROS | [27] |
| $s^4U$ | *S. typhimurium* | NuvA, NuvC | Mutants were sensitive to UV | [28] |
| $s^2U$ | Yeast | Urm1, Nsc2, Nsc6, Tum1, Uba4 | Mutants were sensitive to high temperature, rapamycin, caffeine and oxidative stress | [29, 30] |
| $mcm^5U$/ $ncm^5U$ | Yeast | Elp1-6, Kti11-13, Sit4,SAP185, SAP190, Trm9, Trm112 | Mutants were sensitive to temperature, salt stress, caffeine, Calcofluor, DNA damage agent, oxygen stress, MMS or rapamycin | [31-36] |
| | *A. thaliana* | Elo1-4,AtTrm9, AtTrm112a, AtTrm112b | Mutants were sensitive to ABA and resistant to drought and oxygen stress | [37, 38] |
| | *H. sapiens* | ALKBH8, hTrm9L C8ORF79, Trm112 | Mutants were sensitive to DNA damage agents, ROS and aminoglycoside antibiotics | [39-41] |
| $mcm^5s^2U$ | Yeast | Nsf1, Tum1, Urm1, Uba4, Ncs2, Nsc6, Isu1, Isu2, Cfd1, Cia1, NBP35 | Mutants were sensitive to MMS, $NaAsO_2$, rapamycin, high temperature and thiol-specific oxidants, but resistant to tunicamycin and endoplasmic reticulum stress | [14, 42, 43] |
| $m^5s^2U$ | *T. thermophilus* | TtuA, TtuB | Mutants were sensitive to high temperature | [44] |
| $cmnm^5s^2U$ | *S. mutans* | GidA | Mutants were less tolerant to acid, high osmotic pressure, high temperature, and bacitracin stress | [45] |
| Ψ | Yeast | Pus3 | Mutants were sensitive to temperature | [46] |

[a)] *H. sapiens*: *Homo sapiens*; *A. thaliana*: *Arabidopsis thaliana*; *E. histolytica*: *Entamoeba histolytica*; *T. thermophilus*: *Thermus thermophilus*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. typhimurium*: *Salmonella typhimurium*; *S. mutans*: *Streptococcus mutans*.
[b)] MMS: methyl methanesulfonate; 5-FU: 5-fluorouracil; ABA: abscisic acid; ROS: reactive oxygen species

*trm*1、*trm*4 和 *trm*9 对 $NaAsO_2$ 敏感,而对于 NaOCl 只有 *trm*4 突变体表型出敏感表型。对此结果的解释是,在接触有毒物质时,细胞通过修饰 tRNA 的结构来增加关键蛋白质的合成以使细胞生存。

## 3 胁迫应答中 tRNA 修饰的变化

细胞通过多层次复杂的网络调控基因表达,从而对环境胁迫和异种生物入侵做出响应[13]。有研究表明,胁迫诱导的幸存蛋白质的选择性翻译涉及到 tRNA 转录后修饰的应激特异性变化[14, 15, 33]。如果 tRNA 修饰具有调节作用,那么当细胞生存环境和生理状态发生变化时,某些修饰也会发生一定程度的改变[12]。例如,热菌生活在极端环境中(例如,高温、厌氧、极端 pH 值和高压),在这种条件下,许多抗氧化胁迫、抗高温的酶含量就会发生变化,其中也包括 tRNA 修饰酶[50]。某些情况下,一些修饰的核苷如 D 和 $s^4U$,在高温氧胁迫下会变得不稳定。因此,在嗜热菌中,好氧嗜热细胞需要保护其细胞成分免受氧化应激的影响,而其 tRNA 修饰会对这种应激作出反应[50]。有研究表明,酵母接触化学试剂,如 $H_2O_2$ 或 MMS 后,某些特定的 tRNA 修饰就会增加或减少[14, 33]。2015 年,Chan 等通过 LC-MS/MS 检测了酿酒酵母在 9 种不同的有毒化学试剂处理后,23 种 tRNA 修饰的相对含量有变化,发现除了 $m^5U$ 变化不明显,其余 22 种修饰的核糖核苷都发生了非常显著的变化[13]。Wang 等[20, 23] 对两种模式植物水稻和拟南芥,在不同的逆境处理(干旱、盐胁迫以及冷胁迫)下的核苷修饰变化进行了研究,发现 Am、Cm、$m^1A$ 和 $m^7G$ 这 4 种甲基化核苷在胁迫反应中均发挥重要作用。

## 4 tRNA 修饰响应胁迫在人类疾病研究中的应用

特定 tRNA 修饰系统的缺失可以导致整体或特定 tRNA 修饰水平较低。而研究发现,tRNA 的低修饰在人类中与疾病有关。tRNA 修饰酶在包括癌症和神经系统疾病在内的各种人类疾病中都存在失调。基于对细菌、酵母以及哺乳细胞培养的研究,特定 tRNA 修饰酶以及 tRNA 修饰的缺陷,会使癌细胞对某些特殊的治疗敏感。例如,tRNA-异戊烯转移酶(tRNA-IPT) TRIT1 是 tRNAs(特别是 tRNA-Sec) 37 位 $i^6A$ 修饰,如果敲除 tRNA-IPT 或者缺失 A37 修饰,会降低硒蛋白的含量[27]。而硒蛋白具有 ROS 解毒作用,因此,TRIT1 缺陷型肺腺癌会增加对 ROS 的治疗敏感。同理,人类 hTRM9L 缺陷的结肠直肠癌细胞极易被氨基苷类抗生素杀死[41]。

Keller 等[51] 通过测定人外周血单核细胞对不同修饰的 $tRNA_3^{Lys}$ 的干扰素反应时发现,tRNA-U54 的双甲基化($m^5Um$) 能与 TLR7 协同作用,从而降低人类的免疫应答。变形链球菌(*Streptococcus mutans*)是人类龋齿病的主要病因,研究发现,变形链球菌的 *GidA* 基因对其在逆境条件下的生长非常重要,而这种基因又与变形链球菌的 tRNA 修饰 $cmnm^5s^2U$ 的形成有关[45]。在 *gidA* 缺失突变体中,除了酸性环境外,变形链球菌对其他压力条件包括高渗透压、高温以及杆菌肽压力的承受力明显降低[45]。在人类线粒体细胞中,YRDC 和 OSGEPL1 参与 tRNA-$t^6A37$ 修饰的形成,该修饰对 $CO_2$ 比较敏感,缺失之后会引起某些线粒体疾病[26]。

## 5 tRNA 修饰响应胁迫的可能机制

当细胞遭受不利的环境条件时,应激细胞中基因的整体表达从正常发育模式转变为生存的适应模式,细胞通过激活信号通路和修改基因表达程序来适应不断变化的环境。在裂殖酵母中,有超过 550 种的转录发生上调,同时有多达 450 个基因表达下调[52]。研究表明,胁迫能诱导 20 多种 tRNA 转录后修饰的变化,从而促进关键响应蛋白质密码子偏好 mRNA 的选择性翻译[15, 20, 33]。

研究 *trm* 突变体的胁迫表型与 tRNA 低水平修饰,以及蛋白质合成缺陷之间的关系表明,细胞对压力可能有一个明显的翻译水平的响应[53]。应激反应基因的序列通常对某些氨基酸或同义密码子表现出明显的偏向性。因此,tRNA 修饰与胁迫相关的变化通常被视为是一种适应机制,特别是增加这些基因的表达[54]。例如,在酿酒酵母中,在氧胁迫条件下,会增加 Trm4 介导的 $tRNA^{Leu}$(CAA)第 34 位摇摆碱基 C 甲基化修饰形成 $m^5C$,从而允许选择性翻译与胁迫相关的基因(通常带有 Leu-TTG 密码子)[15]。Trm9 催化的 tRNA 修饰,增强了富含 AGA 和 GAA 转录产物的翻译,这与蛋白质合成、代谢以及逆境信号响应等过程相关[33]。tRNA 甲基转移酶 Alkbh8,能够催化硒代半胱氨酸 tRNA(tRNASec-UGA)摇摆碱基的 $mcm^5U$ 和 $mcm^5Um$ 修饰[55]。在氧胁迫条件下,正常小鼠胚胎成纤维细胞的 tRNA 修饰 $mcm^5Um$ 会增加,以驱动 ROS 解毒酶的表达。而在 *Alkbh*8-/-突变体中,损害诱导的 tRNA 重组和

终止密码子重新编码受到损坏,突变体对氧胁迫表现出非常敏感[40]。

目前的发现并不支持是由于 tRNA 修饰首先调整胁迫相关基因的表达,反而认为是 tRNA 修饰对胁迫信号有直接的作用[56]。在缺失 $mcm^5s^2U$ 的出芽酵母中,发现有 AAA、CAA 和 GAA 密码子的积累,说明当这些密码子进入核糖体 A 位点时,翻译速度变慢,但这些变化的发生不足以影响蛋白质的输出。相反,在突变体中发现,GCN4 介导的应激反应通过一种非常规的途径被激活。因此,由于细胞信号被扰乱,缺失 $mcm^5s^2U$ 会对基因表达产生整体效应[56]。

有研究发现,在真核生物应激反应过程中,细胞内的 tRNA 可以被核糖核酸酶从反密码子环处剪切开,产生 tRNA 来源的片段(tRFs)或 tRNA 来源的应激诱导 RNA(tiRNA)[57-59]。有大量的研究表明,在胁迫条件如氧化胁迫下,拟南芥、酵母和果蝇中的 tRFs 显著增加[18, 57, 60]。在 tRF 的生物发生过程中,Dnmt2 和 Nsun2 催化的 tRNA 甲基化修饰发挥关键作用。Dnmt2 介导的甲基化能够保护 tRNA 不被核糖核酸酶切割。在 *dnmt2* 突变体中,经 $H_2O_2$、亚砷酸盐以及热激处理后,tRFs 明显增加[18]。Blanco 等[17]在 *nsun2* 缺陷型皮肤细胞中发现,有大量的 5′ tRNA 片段存在。在小鼠 *nsun2* 缺失突变体中,缺失 tRNA-$m^5C$ 修饰增加了血管生成素介导的内切核苷酸对 tRNA 的剪切,而积累的 5′ tRNA 碎片会减少蛋白质翻译水平,并激活细胞胁迫途径,从而引起细胞大量的减少并增加皮质、海马和纹状神经元的细胞凋亡。

## 6　问题与展望

tRNA 作为蛋白质合成中不可或缺的参与者,在原核生物和真核生物中是被高度修饰的。这些转录后核苷修饰被赋予了许多细胞功能,从翻译控制到表观遗传调控。编码 tRNA 修饰酶的基因远大于 tRNA 基因本身,这进一步凸显了 tRNA 修饰的重要性[6, 11]。越来越多的研究表明,tRNA 核苷修饰在细胞应激反应和疾病中发挥着重要作用。胁迫诱导的 tRNA 核苷修饰的改变,可以通过影响翻译来调节应激信号通路,从而使细胞可以在胁迫条件下最大限度地生存,这为胁迫应答中的翻译调控提供了一种新的调节机制。随着测序技术及现代生物技术的发展,对 tRNA 的研究涉及到了生物界的各个领域。单细胞真核生物中,对 tRNA 核苷修饰及其修饰酶的研究已经相对完整,而在模式植物拟南芥和人类中,利用基因组测序技术和生物信息学分析手段预测了 tRNA 种类、tRNA 核苷修饰以及相应的核苷修饰酶,但仍需要进一步验证[61, 62]。本文虽然强调了 tRNA 修饰与胁迫响应的可能调节机制,但其具体的机制仍然不清楚。进一步研究 tRNA 核苷修饰在信号通路以及胁迫响应途径中的作用,有利于更好的将 tRNA 功能与整体细胞响应系统联系起来,从而更好的了解细胞是如何对环境做出响应的。

## 参考文献(References)


[1] Machnicka MA, Milanowska K, Osman Oglou O, *et al*. MODOMICS: a database of RNA modification pathways—2013 update [J]. Nucleic Acids Res, 2013, **41**(Database issue): D262-D267

[2] Björk GR, Ericson JU, Gustafsson CE, *et al*. Transfer RNA modification [J]. Annu Rev Biochem, 1987, **56**: 263-287

[3] Agris PF, Vendeix FA, Graham WD. tRNA's wobble decoding of the genome: 40 years of modification [J]. J Mol Biol, 2007, **366**(1): 1-13

[4] Yarian C, Townsend H, Czestkowski W, *et al*. Accurate translation of the genetic code depends on tRNA modified nucleosides [J]. J Biol Chem, 2002, **277**(19): 16391-16395

[5] Urbonavicius J, Qian Q, Durand JM, *et al*. Improvement of reading frame maintenance is a common function for several tRNA modifications [J]. EMBO J, 2001, **20**(17): 4863-4873

[6] Bjork GR, Durand JM, Hagervall TG, *et al*. Transfer RNA modification: influence on translational frameshifting and metabolism [J]. FEBS Lett, 1999, **452**(1-2): 47-51

[7] Agris PF. Decoding the genome: a modified view [J]. Nucleic Acids Res, 2004, **32**(1): 223-238

[8] Motorin Y, Helm M. RNA nucleotide methylation [J]. Wiley Interdiscip Rev RNA, 2011, **2**(5): 611-631

[9] Jin X, Lv Z, Gao J, *et al*. AtTrm5a catalyses 1-methylguanosine and 1-methylinosine formation on tRNAs and is important for vegetative and reproductive growth in Arabidopsis thaliana [J]. Nucleic Acids Res, 2019, **47**(2): 883-898

[10] David R, Burgess A, Parker B, *et al*. Transcriptome-Wide Mapping of RNA 5-Methylcytosine in Arabidopsis mRNAs and Noncoding RNAs [J]. Plant Cell, 2017, **29**(3): 445-460

[11] El Yacoubi B, Bailly M, de Crécy-Lagard V. Biosynthesis and function of posttranscriptional modifications of transfer RNAs [J]. Annu Rev Genet, 2012, **46**: 69-95

[12] Yi C, Pan T. Cellular dynamics of RNA modification [J]. Acc Chem Res, 2011, **44**(12): 1380-1388

[13] Chan CT, Deng W, Li F, *et al*. Highly predictive reprogramming of tRNA modifications is linked to selective expression of codon-biased genes [J]. Chem Res Toxicol, 2015, **28**(5): 978-988

[14] Chan CT, Dyavaiah M, DeMott MS, *et al*. A quantitative systems approach reveals dynamic control of tRNA modifications during cellular stress [J]. PLoS Genet, 2010, **6**(12): e1001247

[15] Chan CT, Pang YL, Deng W, *et al*. Reprogramming of tRNA modifications controls the oxidative stress response by codon-biased translation of proteins [J]. Nat Commun, 2012, **3**: 937

[16] Okamoto M, Fujiwara M, Hori M, *et al*. tRNA modifying enzymes, NSUN2 and METTL1, determine sensitivity to 5-fluorouracil in HeLa cells [J]. PLoS Genet, 2014, **10**(9): e1004639

[17] Blanco S, Dietmann S, Flores JV, *et al*. Aberrant methylation of tRNAs links cellular stress to neuro-developmental disorders [J]. EMBO J, 2014, **33**(18): 2020-2039

[18] Schaefer M, Pollex T, Hanna K, *et al*. RNA methylation by Dnmt2 protects transfer RNAs against stress-induced cleavage

[J]. Genes Dev, 2010, **24**(15): 1590-1595
[19] Hertz R, Tovy A, Kirschenbaum M, *et al.* The Entamoeba histolytica Dnmt2 homolog (Ehmeth) confers resistance to nitrosative stress [J]. Eukaryotic Cell, 2014, **13**(4): 494-503
[20] Wang Y, Li D, Gao J, *et al.* The 2′-O-methyladenosine nucleoside modification gene OsTRM13 positively regulates salt stress tolerance in rice [J]. J Exp Bot, 2017, **68**(7): 1479-1491
[21] Tomikawa C, Yokogawa T, Kanai T, *et al.* N7-Methylguanine at position 46 ($m^7G46$) in tRNA from Thermus thermophilus is required for cell viability at high temperatures through a tRNA modification network [J]. Nucleic Acids Res, 2010, **38**(3): 942-957
[22] Dewe JM, Whipple JM, Chernyakov I, *et al.* The yeast rapid tRNA decay pathway competes with elongation factor 1A for substrate tRNAs and acts on tRNAs lacking one or more of several modifications [J]. RNA, 2012, **18**(10): 1886-1896
[23] Wang Y, Pang C, Li X, *et al.* Identification of tRNA nucleoside modification genes critical for stress response and development in rice and *Arabidopsis* [J]. BMC Plant Biol, 2017, **17**(1): 261
[24] Jaroensuk J, Atichartpongkul S, Chionh YH, *et al.* Methylation at position 32 of tRNA catalyzed by TrmJ alters oxidative stress response in *Pseudomonas aeruginosa* [J]. Nucleic Acids Res, 2016, **44**(22): 10834-10848
[25] Dewe JM, Fuller BL, Lentini JM, *et al.* TRMT1-catalyzed tRNA modifications are required for redox homeostasis to ensure proper cellular proliferation and oxidative stress survival [J]. Mol Cell Biol, 2017, **37**(21). pii: e00214-17
[26] Lin H, Miyauchi K, Tai Harada T, *et al.* $CO_2$-sensitive tRNA modification associated with human mitochondrial disease [J]. Nat Commun, 2018, **9**(1): 1875
[27] Fradejas N, Carlson BA, Rijntjes E, *et al.* Mammalian Trit1 is a tRNA ([Ser] Sec)-isopentenyl transferase required for full selenoprotein expression [J]. Biochem J, 2013, **450**(2): 427-432
[28] Kramer GF, Baker JC, Ames BN. Near-UV stress in Salmonella typhimurium: 4-thiouridine in tRNA, ppGpp, and ApppGpp as components of an adaptive response [J]. J Bacteriol, 1988, **170**(5): 2344-2351
[29] Dewez M, Bauer F, Dieu M, *et al.* The conserved Wobble uridine tRNA thiolase Ctu1-Ctu2 is required to maintain genome integrity [J]. Proc Natl Acad Sci U S A, 2008, **105**(14): 5459-5464
[30] Leidel S, Pedrioli PG, Bucher T, *et al.* Ubiquitin-related modifier Urm1 acts as a sulphur carrier in thiolation of eukaryotic transfer RNA [J]. Nature, 2009, **458**(7235): 228-232
[31] Fellows J, Erdjument-Bromage H, Tempst P, *et al.* The Elp2 subunit of elongator and elongating RNA polymerase ii holoenzyme is a WD40 repeat protein [J]. J Biol Chem, 2000, **275**(17): 12896-12899
[32] Frohloff F, Fichtner L, Jablonowski D, *et al.* *Saccharomyces cerevisiae* Elongator mutations confer resistance to the Kluyveromyces lactis zymocin [J]. EMBO J, 2001, **20**(8): 1993-2003
[33] Begley U, Dyavaiah M, Patil A, *et al.* Trm9-catalyzed tRNA modifications link translation to the DNA damage response [J]. Mol Cell, 2007, **28**(5): 860-870
[34] Patil A, Dyavaiah M, Joseph F, *et al.* Increased tRNA modification and gene-specific codon usage regulate cell cycle progression during the DNA damage response [J]. Cell Cycle, 2012, **11**(19): 3656-3665
[35] Fern ández-Vázquez J, Vargas-Pérez I, Sansó M, *et al.* Modification of tRNA(Lys) UUU by elongator is essential for efficient translation of stress mRNAs [J]. PLoS Genet, 2013, **9**(7): e1003647
[36] Villahermosa D, Fleck O. Elp3 and Dph3 of *Schizosaccharomyces pombe* mediate cellular stress responses through $tRNA^{Lys}_{UUU}$ modifications [J]. Sci Rep, 2017, **7**(1): 7225
[37] Chen Z, Zhang H, Jablonowski D, *et al.* Mutations in ABO1/ELO2, a subunit of holo- Elongator, Increase Abscisic Acid Sensitivity and Drought Tolerance in *Arabidopsis thaliana* [J]. Mol Cell Biol, 2006, **26**(18): 6902-6912
[38] Zhou X, Hua D, Chen Z, *et al.* Elongator mediates ABA responses, oxidative stress resistance and anthocyanin biosynthesis in *Arabidopsis* [J]. Plant J, 2009, **60**(1): 79-90
[39] Fu D, Brophy JA, Chan CT, *et al.* Human AlkB homolog ABH8 is a tRNA methyltransferase required for wobble uridine modification and DNA damage survival [J]. Mol Cell Biol, 2010, **30**(10): 2449-2459
[40] Endres L, Begley U, Clark R, *et al.* Alkbh8 regulates selenocysteine-protein expression to protect against reactive oxygen species damage [J]. PLoS One, 2015, **10**(7): e0131335
[41] Begley U, Sosa MS, Avivar-Valderas A, *et al.* A human tRNA methyltransferase 9-like protein prevents tumour growth by regulating LIN9 and HIF1-alpha [J]. EMBO Mol Med, 2013, **5**(3): 366-383
[42] Goehring AS, Rivers DM, Sprague GF Jr. Attachment of the ubiquitin-related protein Urm1p to the antioxidant protein Ahp1p [J]. Eukaryot Cell, 2003, **2**(5): 930-936
[43] Damon JR, Pincus D, Ploegh HL. tRNA thiolation links translation to stress responses in Saccharomyces cerevisiae [J]. Mol Biol Cell, 2015, **26**(2): 270-282
[44] Shigi N, Sakaguchi Y, Suzuki T, *et al.* Identification of two tRNA thiolation genes required for cell growth at extremely high temperatures [J]. J Biol Chem, 2006, **281**(20): 14296-14306
[45] Li D, Shibata Y, Takeshita T, *et al.* A novel gene involved in the survival of *Streptococcus mutans* under stress conditions [J]. Appl Environ Microbiol, 2014, **80**(1): 97-103
[46] Han L, Kon Y, Phizicky EM. Functional importance of ψ38 and ψ39 in distinct tRNAs, amplified for tRNA-Gln (UUG) by unexpected temperature sensitivity of the $s^2U$ modification in yeast [J]. RNA, 2015, **21**(2): 188-201
[47] Kalhor HR, Clarke S. Novel methyltransferase for modified uridine residues at the wobble position of tRNA [J]. Mol Cell Biol, 2003, **23**(24): 9283-9292
[48] Lu J, Huang B, Esberg A, *et al.* The Kluyveromyces lactis gamma-toxin targets tRNA anticodons [J]. RNA, 2005, **11**(11): 1648-1654
[49] Rubio-Texeira M. Urmylation controls Nil1p and Gln3p-dependent expression of nitrogen- catabolite repressed genes in *Saccharomyces cerevisiae* [J]. FEBS Lett, 2007, **581**(3): 541-550
[50] Hori H, Kawamura T, Awai T, *et al.* Transfer RNA modification enzymes from *Thermophiles* and their modified nucleosides in tRNA [J]. Microorganisms, 2018, **6**(4). pii: E110
[51] Keller P, Freund I, Marchand V, *et al.* Double methylation of tRNA-U54 to 2′-O- methylthymidine (Tm) synergistically decreases immune response by Toll-like receptor 7 [J]. Nucleic Acids Res, 2018, **46**(18): 9764-9775
[52] García P, Encinar Del Dedo J, Ayté J, *et al.* Genome-wide Screening of Regulators of Catalase Expression: Role of a Transcription Complex and Histone and tRNA Modification Complexes on Adaptation to Stress [J]. J Biol Chem, 2016, **291**(2): 790-799
[53] Gu C, Begley TJ, Dedon PC. tRNA modifications regulate translation during cellular stress [J]. FEBS Lett, 2014, **588**(23): 4287-4296
[54] Kirchner S, Ignatova Z. Emerging roles of tRNA in adaptive translation, signalling dynamics and disease [J]. Nat Rev Genet, 2015, **16**(2): 98-112
[55] Songe-Møller L, van den Born E, Leihne V, *et al.* Mammalian ALKBH8 possesses tRNA methyltransferase activity required for the biogenesis of multiple wobble uridine modifications implicated in translational decoding [J]. Mol Cell Biol, 2010, **30**(7): 1814-1827
[56] Zinshteyn B, Gilbert WV. Loss of a conserved tRNA anticodon modification perturbs cellular signaling [J]. PLoS Genet, 2013,

**9**(8): e1003675
[57] Thompson DM, Parker R. Stressing out over tRNA cleavage [J]. Cell, 2009, **138**(2): 215-219
[58] Wang Q, Lee I, Ren J, *et al*. Identification and functional characterization of tRNA-derived RNA fragments (tRFs) in respiratory syncytial virus infection[J].Mol Ther,2013, **21**(2): 368-379
[59] Elkordy A, Mishima E, Niizuma K, *et al*. Stress-induced tRNA cleavage and tiRNA generation in rat neuronal PC12 cells [J]. J Neurochem, 2018, **146**(5): 560-569
[60] Alves CS, Vicentini R, Duarte GT, *et al*. Genome-wide identification and characterization of tRNA-derived RNA fragments in land plants [J]. Plant Mol Biol, 2017, **93**(1-2): 35-48
[61] Chen P, Jäger G, Zheng B. Transfer RNA modifications and genes for modifying enzymes in *Arabidopsis thaliana* [J]. BMC Plant Biol, 2010, **10**: 201
[62] Towns WL, Begley TJ. Transfer RNA methytransferases and their corresponding modifications in budding yeast and humans: activities, predications, and potential roles in *human health* [J]. DNA Cell Biol, 2012, **31**(4): 434-454

# 更　正

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# Corrections & Amendments

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