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氨基酰tRNA合成酶的经典与非经典酶活性*

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摘要 氨基酰tRNA合成酶（aminoacyl-tRNA synthetases，aaRS）家族的经典功能是催化氨基酸与对应tRNA结合，形成氨基酰tRNA，参与蛋白质合成。aaRS在进化过程中不断增加与氨基酰化功能无关的新结构域，其亚细胞器定位也受到营养、压力信号、参与调控血管新生和炎症反应等内外部信号调控，且不同aaRS的突变导致不同人类疾病，提示aaRS具有信号传导功能，但缺少具体的生化机制。最新发现aaRS具有氨基酰转移酶活性。一种氨基酸可以被其对应的aaRS活化成氨基酰AMP，氨基酰AMP可以修饰与该aaRS相互作用蛋白质的赖氨酸，传递该氨基酸的丰度及结构信息，调控细胞信号网络。aaRS新功能的发现和研究，为解释aaRS的生理病理重要性提供新的方向。本文综述aaRS的进化及非经典功能，讨论aaRS氨基酰转移酶活性在细胞信号传导及其与疾病的相关性，也包括药物开发潜力。

关键词 氨基酰tRNA合成酶，氨基酰转移酶，氨基酸信号，疾病
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1 氨基酰tRNA合成酶的进化特征

氨基酰tRNA合成酶（aminoacyl-tRNA synthetases，aaRS）的经典功能是将氨基酸与对应的tRNA分子共价连接，保证蛋白质正常的生物合成。aaRS作为经典酶催化的反应过程大致分为两步：第一步为氨基酸活化，由ATP提供能量生成活化的氨基酰AMP；第二步为活化的氨基酸转移到相应的tRNA 3'端羟基上，生成氨基酰tRNA。低等单细胞生物的aaRS结构相对简单，含有氨基酰化结构域以及tRNA结合结构域。它们将氨基酸活化成氨基酰AMP，以便进一步将氨基酸连接到其对应的tRNA作为蛋白质合成的原料供体。有趣的是，高等生物的aaRS进化出众多新结构域，如WHEP、EMAPII、ELR等，但这些结构域与氨基酰化活性无明显相关性[1]。与此同时，人类中已经发现超过200种新型的aaRS家族剪接异构体，其中大部分已经丧失催化蛋白质合成功能[2]。这些发现提示，aaRS家族蛋白在具有催化形成氨基酰tRNA活性外，还具有其他功能，也就是具有广泛的非经典功能。aaRS的功能异常和突变与包括神经、心血管、肿瘤、纤维化在内的多种人类疾病的发生密切相关（表1），极大地激发了人们对aaRS非经典功能的研究。aaRS功能失调与疾病发生的联系研究取得了很多新的发现。

2 aaRS形成多合成酶聚合物复合体

高等真核生物胞浆中，至少有9种aaRS（GluProRS复合体、IleRS、LeuRS、GlnRS、LysRS、ArgRS、AspRS、MetRS）可以通过氨基酰tRNA合成酶结合的多功能蛋白（aminoacyl tRNA synthetase complex-interacting multifunctional protein，AIMP）作为骨架形成多合成酶聚合物（multisynthetase complex，MSC）。至少有3种AIMP（AIMP1~3）可以作为骨架蛋白形成aaRS聚合物。MSC复合体通过蛋白质相互作用形成，部分揭示了高等生物aaRS进化出更多结构域的必

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要性。已知MSC复合体的生理作用包括：a. 使氨基酰tRNA更快速进入核糖体，提高翻译效率[3-4]；b. 调节aaRS非经典功能的“分子仓库”；c. MSC失调参与感染免疫性疾病以及肿瘤等疾病的病理过程，该过程研究最为深入。除了胞浆中的aaRS形成MSC复合体，线粒体（mt）的aaRS也可以形成线粒体MSC复合体。比如mt-SerRS分别与mt-AlaRS、mt-AsnRS、mt-TyrRS 3种aaRS形成MSC复合体，这些MSC复合体对于特定亚基的氨基酰化活力具有调节作用[5]，线粒体中MSC复合体的其他功能有待更深入的研究。MSC的存在为aaRS失调导致多种疾病提供了有用的提示。

3 aaRS参与生理调控

3.1 传递营养、压力信号

aaRS可作为氨基酸信号的感知器，感知外界氨基酸信号的变化并调控细胞内的生物学过程。例如：LeuRS是胞浆中亮氨酸浓度的感受器，在亮氨酸浓度升高时，LeuRS分别通过激活Vps34-PLD1[6]、EGO复合体[7]和Ras相关的GTP结合蛋白D（RagD）GTPase活性[8]，以及亮氨酰化RagA/B[9]等途径激活mTORC1；mt-ThrRS与mTORC1有共定位，当细胞外苏氨酸浓度升高时，mt-ThrRS通过调节RagA的活性激活mTORC1[10]；当谷氨酰胺浓度升高时，GlnRS与ASK1结合，抑制ASK1促凋亡的作用[11]。

aaRS也会将压力信号传递给下游分子。在低氧环境中，线虫的ThrRS下调核糖体和延伸因子表达，减慢蛋白质翻译，达到节约有限的能量以维持基础代谢的需求[12]，ThrRS这一功能不依赖于转运苏氨酸的量，提示其通过非经典功能调控蛋白质翻译速率；TyrRS可感知氧化压力，氧化压力促进乙酰基转移酶PCAF活性并抑制SIRT1活性，使TyrRS高度乙酰化[13]，入核与TRIM28结合，激活转录因子E2F1，上调DNA损伤修复基因的表达[14]；化合物白藜芦醇可通过其酪氨酸样酚环结构域与TyrRS的活性位点结合，引起TyrRS入核，促进PARP1分子ADP核糖基化，调控下游压力信号通路[15]和自噬[16]，是白藜芦醇发挥抗氧化、神经保护作用的机制之一。另外，MSC复合体中与特异的aaRS结合的AIMP1~3对于MSC复合体的功能也起到关键作用，比如紫外辐射诱导MetRS发生磷酸化，使MSC复合体中与MetRS结合的AIMP3入核调控ATM/ATR的活性，以增加p53的水平，抵抗DNA损伤[17]，同时，AIMP1与AIMP2、ArgRS结合，也作为释放的细胞因子调控血管新生、免疫反应、组织再生、葡萄糖稳态等过程[18]。

3.2 调控血管新生

血管新生由促血管和抗血管生成因子之间的平衡所调控。VEGF信号调节内皮细胞增殖、迁移等过程，在血管新生过程中发挥重要作用[19]。SerRS在非脊椎动物至脊椎动物进化过程中增加的UNE-S结构域含有核定位信号[20]，该核定位信号引导SerRS入核，抑制c-Myc与靶基因*VEGFA*启动子区域结合[21]，从而抑制血管新生。在低氧条件下，SerRS被ATM/ATR磷酸化后与DNA结合减弱，SerRS抑制血管新生的作用减弱[22]。在mt-TrpRS功能缺失的斑马鱼、大鼠模型中，心脏和内皮细胞的血管新生被抑制[23]，IFN-γ刺激一方面使免疫细胞TrpRS通过可变剪切丢失N端47个氨基酸，形成mini-TrpRS，mini-TrpRS作为细胞因子被免疫细胞释放出来，与内皮细胞VE钙黏蛋白结合，抑制血管生成[18, 24]，另一方面，入核的TrpRS通过其WHEP结构域与DNA-PKcs和PARP1同时结合，PARP1使DNA-PKcs发生多聚核糖基化，激活DNA-PKcs的激酶活性，使下游p53发生磷酸化激活，发挥抗血管生成和抗增殖的作用[25]。内皮细胞中mini-TyrRS可通过内皮细胞VEGFR2促进血管生成[26]。此外，TNF-α和VEGF刺激的内皮细胞释放ThrRS，在体外促进内皮细胞迁移和血管新生[27]。在斑马鱼模型中，对应ThrRS和IleRS的突变y58和y68激活UPR通路，VEGFA的表达增加，引起血管生成增加[28]。

4 aaRS变异与疾病

4.1 进行性神经性腓骨肌萎缩症

GlyRS、TyrRS、AlaRS、MetRS、HisRS、TrpRS突变与进行性神经性腓骨肌萎缩症（Charcot-Marie-Tooth disease，CMT）发生相关。导致CMT的GlyRS^{E71G}、GlyRS^{D500N}、GlyRS^{P234KY}、TyrRS^{E196K}突变氨基酰化酶活并未发生改变[29-30]，提示这些突变影响了aaRS的非经典功能。研究表明，与CMT相关的GlyRS[31]、TyrRS[32]、HisRS[33]突变改变了蛋白质构象，相关的HisRS突变所致的构象开放程度与疾病的严重程度呈正相关[33]。发生构象变化的突变蛋白可能会特异性结合新的蛋白质，比如GlyRS^{E71G}、GlyRS^{L129P}等突变

与Nrp1和Trk受体特异性结合，一方面抑制Nrp1与VEGF和结合信号对神经元的保护作用[34]，另一方面使Trk受体失活，影响神经元的发育和分化[35]。GlyRS^{P234KY}突变与HDAC6结合使α微管蛋白（α-tubulin）的乙酰化水平下降，导致突触传递障碍[36]。此外，构象改变的TyrRS突变体入核会结合新的蛋白质，影响神经元的转录调节，可能与疾病的进展相关[37]。另外，GlyRS^{P234KY}、GlyRS^{L129P}、GlyRS^{G240R}会进入应激颗粒（stress granule，SG）中，与SG中核心蛋白G3BP发生异常相互作用，使运动神经元抵御外界不良环境刺激的能力下降，更易发生轴突退变[38]。除了与CMT相关的aaRS点突变导致酶的构象改变，在人类aaRS家族中发现的剪接异构体也呈现与全长aaRS不同的构象，且可能发挥非经典功能。如TyrRS的2个新型剪接异构体形成不同构象的稳定结构，并表现出组织偏向性分布[39]，这可能为一种aaRS突变导致特异靶器官功能异常提供合理的解释。

4.2　肿瘤

aaRS在肿瘤组织中的表达呈现多样性。同一aaRS在不同肿瘤组织类型中可表现为表达上调、下调和不变等。在同种肿瘤组织中不同的aaRS表达变化趋势也不尽相同[40]。aaRS通过调控肿瘤细胞周期、增殖、凋亡及抗肿瘤免疫起作用。在乳腺癌细胞中，GluProRS与转录因子EN1结合，抑制二者结合增加了肿瘤细胞的凋亡[41]。在胃癌细胞中，GluProRS与SYCL2结合，激活WNT/GSK-3β/β连环素（β-catenin）通路，促进增殖和肿瘤生长[42]。在抑癌分子p16^{INK4a}缺失的肿瘤细胞中，MetRS与CDK4结合，通过增强CDK4与分子伴侣HSP90的结合增加CDK4蛋白的稳定性，促进细胞周期进展[43]。此外，MetRS在增殖的细胞中也会入核促进核糖体生物合成[44]，对肿瘤进展起到促进作用。核纤层蛋白（lamin）-integrin-PI3K-p38MAPK信号引起LysRS Thr52位磷酸化，从MSC复合体中释放，定位到细胞膜，与lamin受体67LR结合，增强其稳定性，促进肿瘤细胞的侵袭迁移[45]。LysRS高表达的肿瘤细胞释放GAS6/IL8/ANG等细胞因子，促进肿瘤微环境中M2巨噬细胞极化，促进肿瘤的迁移[46]。TNF-α刺激肿瘤细胞释放的CysRS结合抗原呈递细胞表面的TLR2，可能参与肿瘤免疫[40]。在肿瘤浸润的B细胞中，高表达mt-LeuRS的一群B细胞NAD+再生增强，促进Sirt1对转录因子PAX5的去乙酰化，加强靶基因*TGFβ1*的转录，促进结直肠癌的免疫逃逸[47]。肿瘤细胞释放的FasL引起微环境中巨噬细胞释放GlyRS，GlyRS与肿瘤细胞膜上的CDH6结合引起PP2A释放，使ERK失活，诱导肿瘤细胞死亡[48]。LeuRS在乳腺癌中低表达，相应的亮氨酰-tRNA丰度降低，影响EMP3和GGT5等抑癌蛋白的翻译，进而促进肿瘤发生[49]。此外，多种aaRS的SNP、点突变、移码突变等在急慢性淋巴细胞白血病、乳腺癌、胃癌、结直肠癌等肿瘤中被检测到[40]。

4.3　免疫失调

在免疫激活的肥大细胞中，LysRS被MAPK磷酸化后从MSC复合体中解离，进入细胞核，促进第二信使Ap4A合成，进而激活下游转录因子MITF，促进免疫相关靶基因的转录[50-51]。经过caspase-8切割后，LysRS从MSC复合体中解离，与syntenin蛋白结合，促进肿瘤细胞外泌体释放，引起巨噬细胞迁移和炎症[52]。肿瘤细胞在受到TNF-α刺激后释放的LysRS与巨噬细胞和外周血单核细胞结合，增加TNF-α的生成，增强迁移，以促进免疫反应[53]。在HIV病毒感染过程中，LysRS还可通过其N端结构域与HIV病毒的Gag蛋白C端结构域结合，完成HIV病毒的包装[54]。此外，GluProRS也在病毒感染的过程中发挥调控作用，病毒刺激引起的GluProRS Ser990位磷酸化使GluProRS与PCBP2结合，抑制PCBP2对MVAS信号的负调控作用，从而抑制病毒复制[55]。在骨髓细胞中，IFN-γ刺激使GluProRS Ser999位点发生磷酸化，磷酸化的GluProRS从MSC复合体释放出来，与NSAP1、L13a和GAPDH共同形成GAIT复合体，GAIT复合体与炎症相关基因的3' UTR区域结合，抑制它们的翻译[56-57]。TrpRS也具有免疫调节功能。机体在细菌和病毒感染时，免疫细胞会释放全长的TrpRS，发挥对病原体的先天免疫作用[58-59]。在肿瘤微环境中，色氨酸是免疫细胞发挥功能的重要营养来源，IFN-γ刺激的免疫细胞通过增加TrpRS的表达促进其对色氨酸的吸收[60]，肿瘤细胞的策略是上调降解色氨酸的酶IDO1以利于肿瘤免疫逃逸，同时也上调TrpRS以对抗降解色氨酸带来的营养压力[61]。

抗合成酶综合征（antisynthetase syndrome，ASyS）是一种以出现抗氨基酰tRNA合成酶的自身抗体为特征的自身免疫性疾病，发生于肺间质疾病、肌炎、关节炎、雷诺氏病等。目前有8种抗tRNA合成酶自身抗体在ASyS患者中检测到，其

中HisRS抗体（anti-Jo-1）是最常在ASyS病例中被检测到的抗体[62]，该病发病过程复杂，在人肺组织中检测到大量被颗粒酶B水解的HisRS片段，该片段被自身免疫系统识别，产生anti-Jo-1[63]，而HisRS及被颗粒酶切割的HisRS片段通过CCR5受体招募CD4+、CD8+ T细胞、不成熟的树突状细胞和激活的单核细胞，此过程对ASyS的病程进展起到了重要的推动作用[64]。

4.4 其他疾病

aaRS被报道与纤维化进程相关。纤维化以累积的细胞外基质（ECM）为特征。TGF-β通路激活促进纤维化病理进程，在TGF-β刺激的肺上皮细胞和肝星状细胞中，GluProRS与TGF-β受体、JAKs、STAT3/6形成复合体，促进STAT3/6入核，增加ECM基因的转录，促进肺和肝纤维化过程[65-66]。在心脏压力条件下，GluProRS表达升高，增加富含脯氨酸的蛋白质如胶原、LTBP2、SULF1的翻译，促进心肌纤维化的病理进程[67]。此外，多种致病的线粒体aaRS会导致相应的tRNA水平降低，与HUPRA综合征相关的*SARS2* c.654-14T→A突变使其mRNA发生可变剪接，产生的突变体mt-SerRS与hmtRNA^{Ser}-（AGY）的结合减弱，影响丝氨酰-tRNA的生成。未结合的mtRNA^{Ser}被降解，抑制线粒体呼吸链复合体蛋白如ND3、ATP8等的翻译，线粒体呼吸功能受到抑制，膜电位下降，活性氧（ROS）产生增加[68]；此外，在*NARS2*[69]、*RARS2*[70]、*YARS2*[71]、*LARS2*[72]的致病突变中都检测到了相应tRNA水平的降低。对这些tRNA水平降低的机制和作用的研究有助于阐明线粒体aaRS突变体致病原因，补充有功能的tRNA或氨基酰tRNA可能是治疗相关疾病的策略之一。

5 aaRS的氨基酰转移酶活性

由于很多致病aaRS突变并未影响其识别并活化氨基酸和tRNA的经典活性，aaRS的生理病理重要性长期以来缺少生物化学机制的支撑。这一状况随着aaRS氨基酰tRNA转移酶活性的发现实现了突破。最新发现，aaRS是一个系统的氨基酸感知酶家族，通过识别并将氨基酸修饰到对应的底物蛋白传递各种氨基酸信号。aaRS结合氨基酸，并在aaRS中通过消耗ATP进一步将氨基酸活化成具有生化活性羰基磷酸的氨基酰AMP，aaRS因此可以将其对应的氨基酸修饰到其底物蛋白质赖氨酸[9]。事实上，从原核生物开始，生物就利用含有羰基磷酸分子修饰蛋白质赖氨酸[73]，这一生化机制一直保留到人类，以感知代谢物并传导代谢物信号[74]。aaRS介导的赖氨酸修饰的特异性来自两个层次。首先，每一种aaRS特异识别其对应的氨基酸，并形成特异的氨基酰AMP。其次，由于氨基酰AMP在水溶液中极易被水解，aaRS只修饰那些与aaRS相互作用的蛋白质，而且只有与aaRS相互作用疏水界面的赖氨酸才能够被氨基酸修饰。aaRS在物种进化过程中不断获得新的结构域，且这些结构多是蛋白质相互作用结构域，不排除是为了通过氨基酸修饰更好特异传递氨基酸信号而实现的进化结果。由于氨基酰AMP的浓度反应对应氨基酸的浓度，蛋白质赖氨酸的氨基酰化修饰因此可以将氨基酸丰度，以及氨基酸的侧链空间信息传递到底物蛋白。这一发现为后续研究所证实[75-76]，也为揭示氨基酸特异调控细胞信号通路，以及不同的氨基酸失调导致不同疾病提供了生化基础。

6 总结与展望

尽管aaRS对生物体蛋白质的合成至关重要，但aaRS的非蛋白质合成功能具有更丰富的生理、病理重要性。aaRS已经是药物的靶点，比如抗菌药物莫匹罗星（mupirocin）特异性抑制金黄色葡萄球菌（*Staphylococcus aureus*）IleRS，作为治疗细菌性皮肤感染的抗生素已经被美国食品药品监督管理局（FDA）批准[77]。aaRS非经典功能的发现，尤其是新发现的氨基酰转移酶活性，为aaRS相关疾病的干预提供了更为丰富的靶点。由于aaRS的非蛋白质合成功能多数通过蛋白质相互作用实现，靶向aaRS活性和靶向蛋白质相互作用成为精准和预防性的药物设计的可能。化合物BC-LI-0186阻断LeuRS与RagD的结合[78]，可能作为治疗和缓解mTORC1激活相关肿瘤、肥胖、糖尿病和神经退行性疾病的备选药物。纯化的aaRS或片段甚至可以直接用于治疗相关疾病，比如GlyRS和相关肽的抗肿瘤效果已经在动物模型中得到了证实[79]。可以预见，随着aaRS在多种生理和病理过程中扮演的角色和其中机制的阐明，将推动靶向aaRS精准治疗疾病的药物设计。

Table 1　Diseases related to aaRS mutations

表1　与aaRS突变相关的疾病

疾病	突变的aaRS	症状及病理特征
神经性腓骨肌萎缩症（CMT）	GlyRS[80]、TyrRS[81]、AlaRS[82]、MetRS[83]、HisRS[33]、TrpRS[84]	运动、感觉神经病变
Leigh综合征	mt-AsnRS[69]、mt-IleRS[85]	神经节、丘脑、脑干出现双侧斑块，四肢运动障碍、抽搐，部分突变的病人合并系统性听觉丧失[86]、女性卵巢早衰[69]、生长激素缺乏[87]等
涉及丘脑、脑干和高乳酸的脑白质病（LTBL）	mt-GluRS[88]	发育迟缓，肌张力下降，反射亢进；磁共振成像（MRI）检查可见丘脑、脑干、白质区等异常信号，脑脊液中乳酸水平升高
涉及脑干、脊髓和高乳酸的脑白质病（LBSL）	mt-AspRS[89]	痉挛步态，共济失调，感觉丢失，可由童年期开始进展性发病；MRI检查可见脑室周围白质、锥体束、脊髓中异常信号，脑白质中乳酸水平[90]
脑白质疾病	mt-AlaRS[91]、mt-LeuRS[92] LysRS[92-93]、mt-TrpRS[94]	神经退行性改变，包括共济失调，肌肉痉挛，认知减退；MRI检查可见脑室周围异常白质；所有突变的mt-AlaRS女性病人表现为卵巢功能不全，部分突变的mt-MetRS、mt-LeuRS女性病人出现卵巢功能不全[92，95]
Perrault综合征	mt-HisRS[96]、mt-LeuRS[97]	耳聋（I型），女性卵巢功能异常；学习障碍、外周神经疾病、共济失调（II型）
线粒体心肌病	mt-AlaRS[98]、LysRS[99]、mt-ValRS[100]	心肌肥大，心肌收缩率低，乳酸酸中毒，肌肉样本中线粒体呼吸链复合体表达降低，大部分患者在出生期即发病，死亡率高[98]
HLASA综合征	mt-TyrRS[101]、mt-LeuRS[102]	肌病，乳酸中毒，铁粒幼红细胞性贫血
HUPRA综合征	mt-SerRS[103]	新生儿高尿酸血症，肺动脉高压，肾衰竭，碱中毒
Alper综合征	mt-AsnRS[104]、mt-CysRS[105]、mt-ProRS[104]	发育迟缓；顽固性癫痫；肝功能紊乱
I型糖尿病	mt-AsnRS[106]	婴儿期血糖升高，酮症酸中毒，伴随肌阵挛性抽搐等神经系统损害症状
多系统综合征	PheRS[107]	脑部斑块，肺间质病，面部畸形；系统性炎症
线粒体脑肌病	mt-ThrRS[108-109]、mt-ValRS[108]	肌张力低下，精神运动迟缓，癫痫；mt-ValRS突变的病人可见线粒体呼吸链复合体功能下降[110]、肺动脉高压[111]、乳酸中毒[112]等

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The Canonical and Noncanonical Functions of Aminoacyl−tRNA Synthetases*

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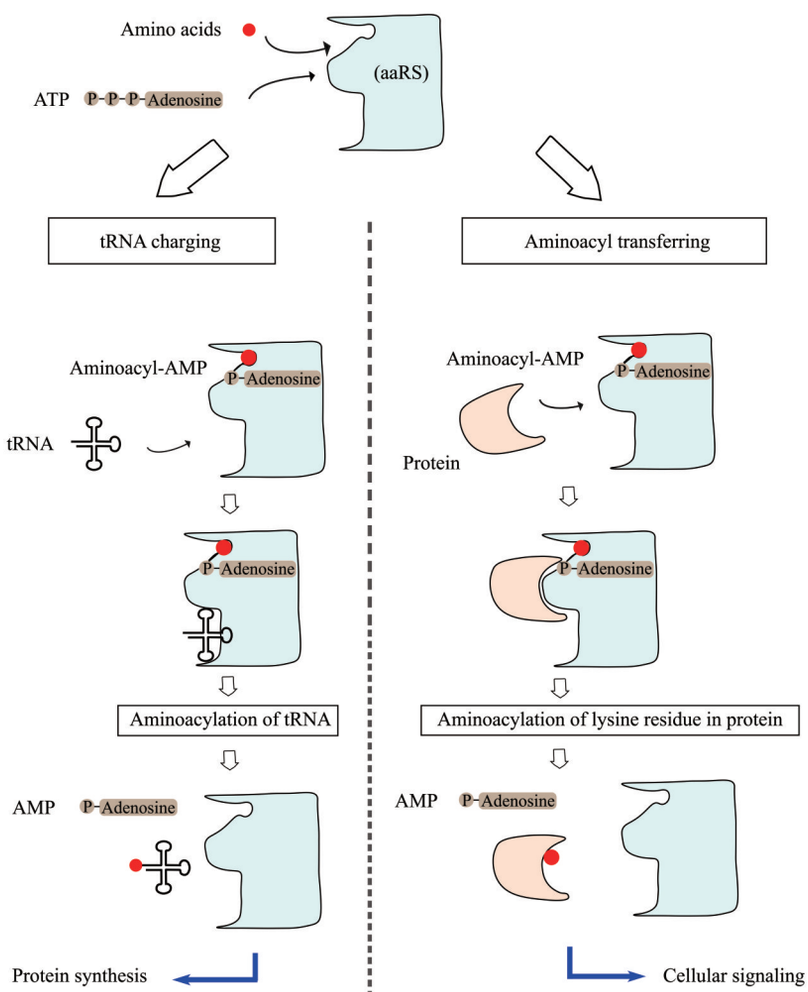
Graphical abstract



Abstract　The canonical functions of aminoacyl-tRNA synthetases (aaRS) are charging amino acids to their cognate tRNAs to ensure the precise protein synthesis. Over the course of evolution, aaRS progressively incorporated domains and motifs that have no essential connections to tRNA charging but play roles in cell signaling. These include mediating protein-protein interaction, protein subcellular localization and sensing and

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transmitting metabolites signals. Deregulated noncanonical aaRS functions are associated with array of human diseases. These all suggest that aaRS play roles beyond their tRNA charging activity, however, the underlying biochemical mechanisms remain to be elucidated. Recent studies revealed that aaRS have aminoacyl transferase activities. An amino acid can be specifically recognized and activated into aminoacyl-AMP by its cognate aaRS, and the formed aminoacyl-AMP in aaRS can modify lysines in proteins that physically interact with this aaRS. This aminoacylation senses and transmits amino acids abundance and side chain information into cell signaling network, provides opportunities to understand why additional domains are acquired by aaRS during evolution and how mutations in an aaRS causes specific human diseases. This review summarizes the noncanonical functions of aaRS and discusses how aaRS mutations may be linked to diseases.

Key words aminoacyl-tRNA synthetases, aminoacyl transferase, amino acid signaling, diseases
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