

· 综述 ·

腺嘌呤核苷酸转位酶:生理功能及在疾病发生中的病理意义

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[摘要] 腺嘌呤核苷酸转位酶(adenine nucleotide translocase, ANT)对线粒体完整性和生物能量代谢至关重要。ANT有4种异构体,生理情况下ANT主要参与膜两侧的腺嘌呤核苷二磷酸/腺嘌呤核苷三磷酸(adenosine diphosphate/adenosine triphosphate, ADP/ATP)交换,可能是构成线粒体渗透性转运孔(mitochondrial permeability transition pore, mPTP)的主要成分,并参与细胞凋亡和质子泄漏过程。ANT损伤引起线粒体功能障碍,在代谢性疾病、心肌病及肿瘤发生进展中有着重要的病理意义,文章总结了近几年有关ANT的研究进展和知识,旨在为靶向ANT的疾病治疗提供新思路。

[关键词] 腺嘌呤核苷酸转位酶;代谢性疾病;恶性肿瘤;心肌病;线粒体;ADP/ATP载体;腺嘌呤核苷酸载体

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Adenine nucleotide translocase: physiological functions and pathological significance in disease occurrence

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[Abstract] Adenine nucleotide translocases (ANTs) are crucial for mitochondrial integrity and bioenergetic metabolism. There are four isoforms of ANTs. Under physiological conditions, ANTs primarily engage in the exchange of adenosine diphosphate (ADP) and adenosine triphosphate (ATP) across mitochondrial membranes. ANT isoforms are also potentially significant components of the mitochondrial permeability transition pore (mPTP), contributing to processes such as cellular apoptosis and proton leakage. Impairment of ANTs leads to mitochondrial dysfunction, which holds significant pathological implications in metabolic diseases, cardiomyopathies, and cancer progression. This review summarizes recent advancements and knowledge regarding ANTs, aiming to offer new insights into potential therapeutic strategies targeting ANTs in diseases.

[Key words] adenine nucleotide translocase; metabolic disease; malignant tumor; cardiomyopathy; mitochondrial; ADP/ATP carrier; adenine nucleotide carrier

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腺嘌呤核苷酸转位酶(adenine nucleotide translocase, ANT),或称线粒体ADP/ATP载体(mitochondrial ADP/ATP carrier, AAC)、腺嘌呤核苷酸载体(adenine nucleotide carrier, ANC),约占内膜蛋白总量的10%,广泛分布于线粒体内膜^[1]。ANT主要负责将ADP导入线粒体基质,并将新合成的ATP输出到细胞质,这一过程将细胞产能和耗能过程联系起来^[2]。ANT

在维持线粒体正常功能方面发挥着重要作用,由各类损伤因素引起的ANT功能障碍可以引起多种疾病,如代谢性疾病、肿瘤及心肌病等^[3-5],因此本文对最近有关ANT异构体性质和致病机制的报道进行综述。

1 ANT的异构体

在人体中,由溶质载体(solute carrier, SLC)蛋白家族基因编码^[6]的ANT有4类异构体,即ANT1、ANT2、ANT3、ANT4。ANT异构体的表达具有组织

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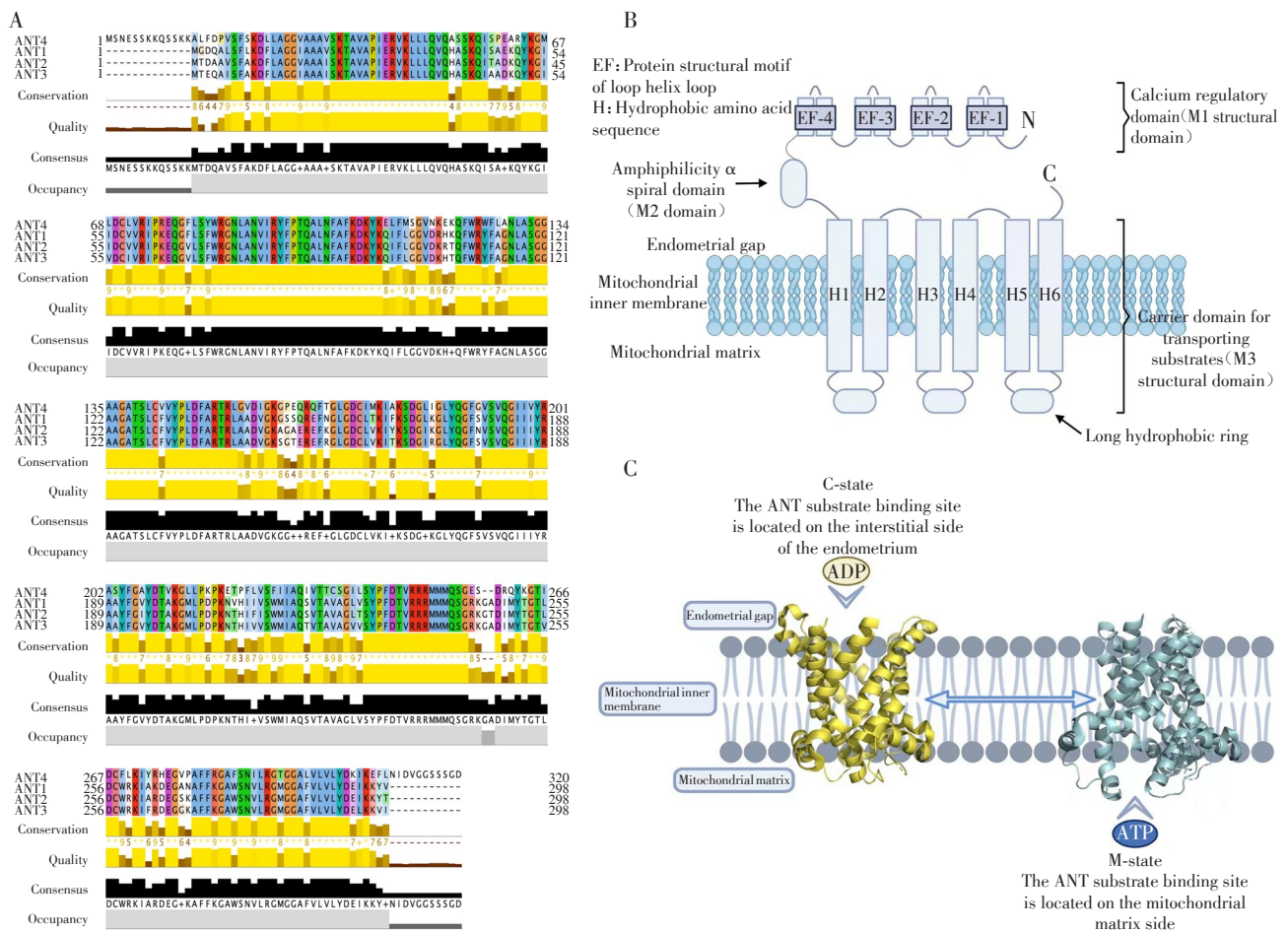
细胞特异性, 使用实时荧光定量聚合酶链式反应 (real-time polymerase chain reaction, real-time PCR) 的方法检测ANT的分布丰度可以发现, ANT1在心脏、骨骼中表达水平较高, ANT2主要表达于具有强增殖能力的细胞, 如癌细胞、肝细胞、神经干细胞等, 而ANT3普遍表达于所有组织细胞中, ANT4则在肝脏和睾丸组织中高表达。通过序列比对发现, ANT各类异构体之间同源性很高, 其中相同的氨基酸序列占67.8%, 相似的氨基酸序列占83.2%(图1A)^[7]。

2 ANT的结构

作为一类跨膜蛋白, ANT跨膜区域由6个高度保守的排列形成 α 螺旋的疏水性氨基酸序列(H1~H6)构成^[6, 8]。在线粒体内膜的基质侧, 相邻的2个疏水氨基酸序列间通过与细胞膜平行的包含短矩阵螺旋的长疏水环相连接。研究表明, ANT通常由3个结构域组成: 1个N末端的含有4个EF

手(一种环-螺旋-环的蛋白结构基序, 能够结合钙离子并引起构象改变)的钙调节域(M1)、1个两亲性 α 螺旋结构域(M2)以及1个C末端用于运输底物的载体域(M3)。ANT1、ANT2、ANT3都具有这3种结构域, 而ANT4则缺乏钙调节域(图1B)^[9-10]。

ANT具有两种不同的功能形态: M态(mitochondrial matrix-state, M-state)^[11]和C态(cytoplasmic-state, C-state)。在M态下, ANT底物结合位点暴露在线粒体基质侧, 负责输送ATP到细胞质, 为细胞供能; 而在C态下, ANT底物结合位点位于内膜间隙侧, 将ADP转运回线粒体内, 从而为线粒体接下来的底物循环做准备(图1C)。现有研究表明, ANT的功能形态转变与一些化学物质相关, 如植物源的羧基苍术苷(carboxyatractyloside, CATR)和细菌源的米醇菌酸(bongkrelic acid, BKA), CATR可以从内膜间隙侧结合到ANT, 促使ANT转变为C态, 而BKA则从基质侧结合到ANT, 形成M态ANT^[12-13]。



A: Multiple sequence alignment analysis of ANT isoforms^[7]. B: Domain display of ANT isoforms^[10]. C: Demonstration of functional and morphological transformation of ANT isoforms^[11].

图1 ANT异构体的序列、结构、功能形态变化

Figure 1 Sequence, structure, and functional morphological changes of ANT isoforms

3 ANT的生理功能

3.1 ANT通过调节线粒体膜电位影响细胞凋亡

ANT是位于线粒体内外膜之间的线粒体渗透性转运孔(mitochondrial permeability transition pore, mPTP)的主要组成部分,与细胞凋亡密切相关。目前,mPTP分子组成尚未完全清楚,多数学者认为其是由ANT、胞质苯二氮卓受体、孔蛋白/电压依赖性阴离子通道(voltage-dependent anion channel,VDAC)、肌酸激酶、B细胞淋巴瘤/白血病-2相关X蛋白(B cell lymphoma/leukemia - 2 associated X protein, Bax)以及基质环磷酸蛋白-D(cyclophilin-D, CypD)构成。mPTP开放与关闭可以导致线粒体膜电位(mitochondrial transmembrane potential, MMP/ $\Delta\Psi_m$)变化,而 $\Delta\Psi_m$ 的变化影响线粒体膜极化程度,进而影响下游凋亡事件的发生,如 $\Delta\Psi_m$ 减低可以使线粒体膜发生去极化,引起下游细胞色素c的释放,进而引起胞内胱天蛋白酶(cysteinyI aspartate specific proteinase, caspase)家族的级联激活,从而诱发细胞凋亡,与之相反, $\Delta\Psi_m$ 升高可以阻止凋亡事件的发生,发挥对细胞的保护作用^[13]。ANT各类异构体在细胞凋亡过程中发挥着不同作用,ANT3和ANT1通常表现出强促凋亡特性。与之相反,ANT2与ANT4抑制细胞凋亡,对细胞起保护作用^[14]。ANT异构体的这种特性与其在线粒体内膜两侧交换ADP和ATP的方向有关,研究表明,ANT1和ANT3通过质子梯度和ATP合酶将有氧呼吸产生的ATP转运至内膜的胞质侧,而ANT2异构体主要负责将无氧糖酵解过程中由葡萄糖-6-磷酸(glucose 6-phosphate, G6P)产生的ATP转运至线粒体基质侧。值得注意的是,ANT1和ANT3过表达会导致 $\Delta\Psi_m$ 降低,引起线粒体去极化,最终导致细胞凋亡,与之相反,ANT2过表达时会进行ATP的逆向运输,有助于维持 $\Delta\Psi_m$,从而抑制细胞凋亡^[7]。

3.2 ANT参与线粒体质子泄漏过程进而调节细胞能量代谢

线粒体氧化磷酸化过程伴随着电子沿着呼吸链的一系列载体传递。在这种“电子传递”过程中,质子被电子传递链所释放的能量泵出线粒体内膜,产生跨线粒体内膜的质子动力(proton-motive force, Δp),在质子回流过程中, Δp 与ATP合成偶联,产生细胞活动所需能量。然而,一部分质子在回流过程中通过旁路途径进入线粒体基质,与ATP合成解偶,产生的能量以热能的形式消耗,这一过程被称

为质子泄漏^[15-16]。尽管目前对于质子泄漏的机制研究并不完善,解偶联蛋白(uncoupling protein, UCP)和ANT已经被证明参与了线粒体质子泄漏过程。UCP主要包括UCP1、UCP2和UCP3,在被脂肪酸或膜磷脂过氧化产生的烯醛激活时,会引起质子泄漏。ANT与UCP1具有20%的同源性^[7],研究表明,ANT1直接参与了肌细胞和棕色脂肪线粒体中的高基础质子泄漏过程^[17]。而与ANT1不同,ANT2介导的质子泄漏需要游离脂肪酸参与^[18],目前,有关ANT参与质子泄漏过程的机制研究较少,ANT异构体在质子泄漏过程中的具体作用机制需要进一步研究。

4 ANT与疾病

4.1 ANT与代谢相关疾病

代谢相关疾病是一组与体内代谢过程异常相关的疾病,这些异常可以涉及体内的能量生成、物质代谢和激素调节等多个方面,代谢相关疾病通常包括糖尿病、肥胖症、代谢相关性肝病、高尿酸血症、高血压等^[19]。近年来研究表明,ANT与代谢相关疾病的发生及进展相关。

4.1.1 ANT与糖尿病及肥胖症

糖尿病是以高血糖为特征的慢性代谢性疾病,2017年全球糖尿病患者人数已超过4.25亿,而我国的糖尿病患者人数已超过1.14亿,约占全球糖尿病患者总数的1/4,由于糖尿病已成为威胁人类健康的重要问题,需要寻找糖尿病治疗的新靶点。Morrow等^[20]通过构建ANT1敲除(ANT1^{-/-})小鼠发现,与野生型小鼠相比,ANT1^{-/-}小鼠表现出胰岛素抵抗的改善及糖耐受的提高,并且其肌组织糖尿病相关基因的表达下调,值得注意的是,Moon等^[21]的ANT2敲除实验也印证了该结论,ANT2^{-/-}小鼠表现出相似的胰岛素敏感性提高及糖耐量改善。

临床研究报告显示,肥胖症患者的糖尿病患病率是正常范围体重者的3倍^[22]。肥胖症与糖尿病的发生密切相关,ANT2可以引起游离脂肪酸诱导的线粒体通透性转变,导致肥胖症小鼠脂肪组织巨噬细胞(adipose tissue macrophage, ATM)的促炎激活,进而诱发活性氧的产生和组织炎症损伤,并最终带来体重增加、血糖水平升高、胰岛素抵抗加重的不良预后^[21]。

4.1.2 ANT与代谢相关性肝病

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)[目前已更名为代谢相关脂肪性

肝病^[23] (metabolic dysfunction - associated fatty liver disease, MAFLD)]是指患者每日酒精摄入量小于20 g, 排除其他引起肝损的病因, 以肝细胞内脂肪过度沉积为主要特征的代谢性疾病。如果不加以外界干预, mAFLD患者很容易从非酒精性脂肪肝进展至非酒精性脂肪性肝炎及其相关纤维化, 最后发展为肝硬化和肝细胞癌。在一般人群中mAFLD患病率为25%~30%。目前, mAFLD已成为全球范围内最常见的慢性肝病^[24-25]。

ANT与mAFLD的发生进展有关, Cho等^[26]通过靶向敲除小鼠肝脏细胞ANT2发现, 在不损害线粒体完整性和小鼠肝功能的情况下, 敲除ANT2可以增强小鼠肝脏细胞线粒体解偶联呼吸功能, 进而加速肝脏细胞脂肪代谢、减轻肝脏脂肪堆积。Zhang等^[27]则进一步用苍术苷(atractyloside, ATR)特异性抑制ANT2发现, 抑制ANT2可以延缓小鼠肝脏细胞脂肪变进程。这为有针对性地改善肝脏线粒体代谢, 特别是通过抑制ANT治疗mAFLD提供了新见解。

4.2 ANT与肿瘤

恶性肿瘤是细胞不受控制地增殖、伴有或不伴其他组织侵袭的一类疾病, 根据世界卫生组织报道, 截至2030年预估会有1 310万人死于恶性肿瘤^[28]。由于ANT亚型的分布差别和功能差异, 本篇将分别阐释它们与肿瘤的关系。

4.2.1 ANT1

ANT1在体内和体外实验中都表现出强大的抗肿瘤活性。ANT1在大多数恶性肿瘤中低表达, 它的这种抗肿瘤特性可能与其在线粒体内膜上与mPTP调节剂CypD、p53的关联有关, 而p53-CypD-ANT1关联是细胞程序性坏死级联激活的关键初始步骤^[29]。研究表明, 在宫颈癌细胞中, 使用鞘氨醇激酶(sphingosine kinase 1/2, SphK1/2)抑制剂诱导这种关联可以显著抑制癌细胞生长^[30]。在非小细胞肺癌中, ASP4132[一种高效的腺苷单磷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)激动剂]通过激活AMPK信号也可以促进p53-CypD-ANT1关联, 进而诱导肿瘤细胞凋亡^[31]。此外, ANT1构象改变促进mPTP开放也是其抗肿瘤特性的潜在机制。EB病毒潜伏膜蛋白(Epstein-Barr virus latent membrane protein 1, EBV-LMP1)可以通过与ANT1结合抑制mPTP开放从而介导癌细胞耐药^[32]。EBV-LMP1表达阳性的鼻咽癌病例对使用顺铂的化疗方案敏感性较差, ANT1构象抑制剂CATR联合顺铂可改善

EBV-LMP1阳性细胞的化疗敏感性, 这一发现证实了ANT1可能是未来克服肿瘤对化疗药物耐药的一个新靶点。

4.2.2 ANT2

与ANT1不同, ANT2被确定为癌细胞中的一种抗凋亡因子。它在各种类型的癌症中高水平表达, 包括神经母细胞瘤^[33]、肝癌^[34]、前列腺癌^[35]等。ANT2在维持癌细胞生存方面具有关键作用, 目前已成为癌症治疗的一个备受瞩目的潜在靶点。研究表明, ANT2的高表达是TP53(tumor protein P53)突变型神经母细胞瘤预后不良的强有力预测因子。同时, 使用4-[N-(S-青霉胺乙酰基)氨基]-苯基亚肿酸抑制ANT2表达可以TP53剂量依赖的方式促进肿瘤细胞凋亡^[33]。ANT2在前列腺癌组织中的表达显著上调, 敲除ANT2可以有效抑制肿瘤细胞的增殖、迁移和侵袭。ANT2位于肿瘤细胞生存与凋亡的“十字通路”, 众多影响肿瘤细胞命运的分子都与ANT2存在直接或间接关联。研究表明, 磷酸甘油酸脱氢酶与ANT2直接相互作用, 进而提高肿瘤细胞线粒体核糖体再循环效率, 增加肿瘤细胞的代谢活力^[34-35]。抗菌肽TP4(teleost piscidins-4)通过靶向ANT2诱导肿瘤细胞线粒体功能障碍, 进而发挥抗肿瘤活性^[36]。丁酸钠(sodium butyrate, NaB)在药理剂量(>2.5 mmol/L)下可诱导胶质瘤细胞凋亡, 这种抗肿瘤活性依赖ANT2的活化^[37]。总之, ANT2是与癌细胞生存和凋亡抵抗密切相关的蛋白质, 针对ANT2或其相关途径有望成为癌症治疗的一个潜在方向。

4.2.3 ANT3

ANT3与细胞凋亡过程相关, 过表达ANT3能够促进 $\Delta\Psi_m$ 去极化和Caspase 9的激活, 从而促进凋亡的发生^[38]。最近Hao等^[39]报道了ANT3作为可能的标志物, 具有用于宫颈癌早期检测的潜在价值, 这为宫颈癌的早期诊断提供了新的研究方向。

4.2.4 ANT4

ANT4被划分为抑制肿瘤凋亡的线粒体蛋白, 其可能机制与阻断或延迟Caspase 9的凋亡作用、下调B淋巴细胞瘤-2(B cell lymphoma/leukemia-2, BCL-2)表达有关, 目前这方面的报道较少, 相关机制需要进一步的实验研究挖掘^[40]。

4.3 ANT与心肌病

心肌病是一类与心脏肌肉病变有关的疾病, 其常见类型包括扩张型^[41]、肥厚型^[42]、限制型^[43], 此外, 还包括应激型^[44]及致心律失常性右室心肌

病^[45]。心肌病往往与心脏功能失常关联,引起液体滞留和循环超载,进而导致心肌部分功能区域血液供应中断,并最终导致该区域的心肌细胞死亡^[46]。2013年发布的一份全球性疾病负担调查报告显示,约有250万人罹患心肌炎、心肌病变^[47],心肌病作为一种相对常见的心脏疾病,可影响各年龄段的人群,并且其中一些类型还具有遗传性,心肌病可以导致严重的心脏功能障碍,包括心力衰竭和恶性心律失常,因此,对心肌病的早诊断、早治疗对改善患者预后至关重要。

ANT与心肌病变关系密切。ANT在线粒体内膜上的异构转变影响心肌细胞正常功能,有研究表明,ANT在心肌炎和限制性心肌病患者心肌细胞中发生了异构转变,具体表现为ANT1异构体的增加和ANT2异构体的减少,而ANT3的水平保持不变,这一变化可以引起线粒体功能障碍,进而导致细胞能量代谢紊乱^[48]。

虽然心肌细胞普遍表达ANT异构体,但ANT1的含量仍占据主导地位,ANT1突变及其表达水平或活性降低已被确认与严重的心脏疾病相关^[49]。ANT1^{-/-}基因敲除小鼠通常表现为进行性心肌肥厚和左心室壁增厚^[50],并且这种小鼠更容易进展为心脏衰竭甚至发生心源性猝死^[51],这与其心肌细胞内活性氧的产生增加和氧化磷酸化抑制有关^[52]。近期研究发现,ANT1可能参与心肌细胞内线粒体呼吸链超复合物(respiratory chain supercomplexes, RCS)的组装,ANT1表达降低可以导致RCS在H9c2心肌前体细胞中的解离,进而引起线粒体ATP/ADP运输功能受损,这可能是ANT1水平下降引发心脏病变的原因^[53]。

ANT1过表达发挥心肌保护作用。ANT1过表达可以引起ATP/ADP运输增加、呼吸链复合物活性提高,从而预防高血压引起的心肌肥厚及纤维化、显著改善左心舒缩功能甚至逆转心肌重构。此外,ANT1过表达引起细胞色素c、caspase 3水平降低,使mPTP开放延迟,稳定 $\Delta\Psi_m$,从而减轻细胞凋亡。研究表明,ANT1过表达与细胞外信号调节激酶1/2和蛋白激酶B的激活相关,这两种激酶与缺氧诱导因子1 α (hypoxia-inducible factor 1 α , HIF-1 α)的高水平表达有关,后者可以通过诱导糖酵解途径来稳定 $\Delta\Psi_m$ 进而维持细胞生存^[51]。此外,ANT1可以通过经典的转化生长因子 β (transforming growth factor β , TGF β)/SMAD信号通路调节心肌细胞存活。在经典的TGF β /SMAD信号通路中,TGF II型受

体与I型受体相互作用,形成一个复合体,磷酸化激活SMAD2和SMAD3。活化的SMAD2和SMAD3连同SMAD4一起转移到细胞核内,调控靶基因的转录^[54]。ANT1过表达能够使TGF β 1表达下调,进而抑制细胞凋亡相关的死亡相关蛋白激酶和TGF β 1信号调节蛋白SMAD7表达,从而干扰细胞凋亡进程^[55],ANT1在心肌病病理生理学中发挥的重要作用使其成为心肌病治疗的潜在靶点。

5 总结与展望

ANT作为线粒体内膜上的关键蛋白,在细胞生物学中扮演着多种角色。ANT具有4种不同的异构体,即ANT1、ANT2、ANT3和ANT4,它们在不同的组织和细胞中表达水平和功能各不相同。ANT是参与构成促凋亡的mPTP的主要部分,并与线粒体质子泄漏过程相关。ANT的功能障碍与多种疾病的发生有着密切关系,包括糖尿病、肥胖症、代谢性肝病等。

ANT在细胞代谢和凋亡中的重要作用使其成为多种疾病研究的焦点。未来的研究应当深入探索ANT在各类疾病发展中的具体机制,针对已知可调控ANT活性的特定分子和药物,深入研究它们与ANT的相互作用及其作为治疗剂的可能性。此外,可以通过CRISPR等基因编辑技术干预ANT表达,研究其对细胞和生物个体健康和疾病状态的影响,这可能成为新的研究方向。同时,探讨ANT与线粒体及其他细胞器之间的相互作用网络,将有助于我们理解其在细胞功能中的作用以及在疾病发展中的地位。在疾病诊断方面,ANT表达或功能变化作为生物标志物的潜力也值得进一步探索。此外,通过人群和流行病学研究分析ANT基因突变与特定健康状况或疾病风险的关系,不仅可以加深我们对ANT在人类健康中作用的理解,也为未来针对ANT的疾病治疗策略提供了新的方向。这一系列综合性研究将极大推动我们对ANT功能及其在人类疾病中作用的认识,为发现新的诊断工具和治疗手段提供强有力的科学基础。

[参考文献]

- [1] CIMADAMORE - WERTHEIN C, JAIQUEL BARON S, KING M S, et al. Human mitochondrial ADP/ATP carrier SLC25A4 operates with a ping-pong kinetic mechanism [J]. EMBO Rep, 2023, 24(8): e57127
- [2] HOOGSTRATEN C A, JACOBS M M E, DE BOER G, et al. Metabolic impact of genetic and chemical ADP/ATP

- carrier inhibition in renal proximal tubule epithelial cells [J]. *Arch Toxicol*, 2023, 97(7): 1927-1941
- [3] XIAO P, CHEN X, DONG Z, et al. BNIP3 overexpression may promote myeloma cell apoptosis by enhancing sensitivity to bortezomib via the p38 MAPK pathway [J]. *Hematology*, 2023, 28(1): 2231739
- [4] GRELL H, WOZNICA D, RATAJCZAK K, et al. Mitochondrial dynamics in neurodegenerative diseases: unraveling the role of fusion and fission processes [J]. *Int J Mol Sci*, 2023, 24(17): 13033
- [5] JI C, ZHANG Z, LI Z, et al. Mitochondria-associated endoplasmic reticulum membranes: inextricably linked with autophagy process [J]. *Oxid Med Cell Longev*, 2022, 2022: 7086807
- [6] RUPRECHT J J, KUNJI E R S. The SLC25 mitochondrial carrier family: structure and mechanism [J]. *Trends Biochem Sci*, 2020, 45(3): 244-258
- [7] CHEN Y, WU L, LIU J, et al. Adenine nucleotide translocase: current knowledge in post-translational modifications, regulations and pathological implications for human diseases [J]. *FASEB J*, 2023, 37(6): e22953
- [8] RUPRECHT J J, KING M S, ZÖGG T, et al. The molecular mechanism of transport by the mitochondrial ADP/ATP carrier [J]. *Cell*, 2019, 176(3): 435-447
- [9] OGUNBONA O B, CLAYPOOL S M. Emerging roles in the biogenesis of cytochrome c oxidase for members of the mitochondrial carrier family [J]. *Front Cell Dev Biol*, 2019, 7: 3
- [10] HARBORNE S P D, KUNJI E R S. Calcium-regulated mitochondrial ATP-Mg/Pi carriers evolved from a fusion of an EF-hand regulatory domain with a mitochondrial ADP/ATP carrier-like domain [J]. *IUBMB Life*, 2018, 70(12): 1222-1232
- [11] MONTALVO-ACOSTA J J, KUNJI E R S, RUPRECHT J J, et al. Structure, substrate binding, and symmetry of the mitochondrial ADP/ATP carrier in its matrix-open state [J]. *Biophys J*, 2021, 120(23): 5187-5195
- [12] RUPRECHT J J, KUNJI E R. Structural changes in the transport cycle of the mitochondrial ADP/ATP carrier [J]. *Curr Opin Struct Biol*, 2019, 57: 135-144
- [13] MISHRA G, COYNE L P, CHEN X J. Adenine nucleotide carrier protein dysfunction in human disease [J]. *IUBMB Life*, 2023, 75(11): 911-925
- [14] ZAIB S, HAYYAT A, ALI N, et al. Role of mitochondrial membrane potential and lactate dehydrogenase a in apoptosis [J]. *Anticancer Agents Med Chem*, 2022, 22(11): 2048-2062
- [15] HERRNHOLD M, HAMP I, PLETTENBURG O, et al. Adverse bioenergetic effects of N-acyl amino acids in human adipocytes overshadow beneficial mitochondrial uncoupling [J]. *Redox Biol*, 2023, 66: 102874
- [16] NESCI S. Proton leak through the UCPs and ANT carriers and beyond: a breath for the electron transport chain [J]. *Biochimie*, 2023, 214(Pt B): 77-85
- [17] BRAND M D, PAKAY J L, OCLLOO A, et al. The basal proton conductance of mitochondria depends on adenine nucleotide translocase content [J]. *Biochem J*, 2005, 392(Pt 2): 353-362
- [18] SHABALINA I G, KRAMAROVA T V, NEDERGAARD J, et al. Carboxyatractyloside effects on brown-fat mitochondria imply that the adenine nucleotide translocator isoforms ANT1 and ANT2 may be responsible for basal and fatty-acid-induced uncoupling respectively [J]. *Biochem J*, 2006, 399(3): 405-414
- [19] PESTEL J, BLANGERO F, WATSON J, et al. Adipokines in obesity and metabolic-related-diseases [J]. *Biochimie*, 2023, 212: 48-59
- [20] MORROW R M, PICARD M, DERBENEVA O, et al. Mitochondrial energy deficiency leads to hyperproliferation of skeletal muscle mitochondria and enhanced insulin sensitivity [J]. *Proc Natl Acad Sci USA*, 2017, 114(10): 2705-2710
- [21] MOON J S, DA CUNHA F F, HUH J Y, et al. ANT2 drives proinflammatory macrophage activation in obesity [J]. *JCI Insight*, 2021, 6(20): e147033
- [22] GELONEZE B, VASQUES A C J, STABE C F C, et al. HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome: Brazilian Metabolic Syndrome Study (BRAMS) [J]. *Arquivos Brasileiros De Endocrinol E Metabol*, 2009, 53(2): 281-287
- [23] ESLAM M, NEWSOME P N, SARIN S K, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement [J]. *J Hepatol*, 2020, 73(1): 202-209
- [24] RINELLA M E, NEUSCHWANDER -TETRI B A, SIDDIQUI M S, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease [J]. *Hepatology*, 2023, 77(5): 1797-1835
- [25] TENG M L, NG C H, HUANG D Q, et al. Global incidence and prevalence of nonalcoholic fatty liver disease [J]. *Clin Mol Hepatol*, 2023, 29(Suppl): S32-S42
- [26] CHO J, ZHANG Y, PARK S Y, et al. Mitochondrial ATP transporter depletion protects mice against liver steatosis and insulin resistance [J]. *Nat Commun*, 2017, 8: 14477
- [27] ZHANG P F, CHENG X Y, SUN H M, et al. Atractyloside protect mice against liver steatosis by activation of autophagy

- gy via ANT-AMPK-mTORC1 signaling pathway[J]. *Front Pharmacol*, 2021, 12: 736655
- [28] SAHOO G, SAMAL D, KHANDAYATARAY P, et al. A review on caspases: key regulators of biological activities and apoptosis[J]. *Mol Neurobiol*, 2023, 60(10): 5805–5837
- [29] ZHANG Y, LIU S, MA J L, et al. Apocynum venetum leaf extract alleviated doxorubicin - induced cardiotoxicity through the AKT/Bcl-2 signaling pathway[J]. *Phytomedicine*, 2022, 94: 153815
- [30] ZHANG Y, CHENG L, SHI X, et al. The sphingosine kinase inhibitor SKI - V suppresses cervical cancer cell growth[J]. *Int J Biol Sci*, 2022, 18(7): 2994–3005
- [31] XIA Y C, ZHA J H, SANG Y H, et al. AMPK activation by ASP4132 inhibits non - small cell lung cancer cell growth[J]. *Cell Death Dis*, 2021, 12(4): 365
- [32] ZHAO L, DENG X, LI Y, et al. Conformational change of adenine nucleotide translocase-1 mediates cisplatin resistance induced by EBV-LMP1[J]. *EMBO Mol Med*, 2021, 13(12): e14072
- [33] SENEVIRATNE J A, CARTER D R, MITTRA R, et al. Inhibition of mitochondrial translocase SLC25A5 and histone deacetylation is an effective combination therapy in neuroblastoma[J]. *Int J Cancer*, 2023, 152(7): 1399–1413
- [34] SHU Y, HAO Y, FENG J, et al. Non-canonical phosphoglycerate dehydrogenase activity promotes liver cancer growth via mitochondrial translation and respiratory metabolism[J]. *Embo J*, 2022, 41(23): e111550
- [35] ZHANG H Y, CHEN N H, DENG Z H, et al. Suppression of ANT2 by miR-137 inhibits prostate tumorigenesis[J]. *Front Genet*, 2021, 12: 687236
- [36] SU B C, LIU Y C, TING C H, et al. Antimicrobial peptide TP4 targets mitochondrial adenine nucleotide translocator 2[J]. *Mar Drugs*, 2020, 18(8): E417
- [37] QIN X J, XU Y H, PENG S Q, et al. Sodium butyrate opens mitochondrial permeability transition pore (MPTP) to induce a proton leak in induction of cell apoptosis[J]. *Biochem Biophys Res Commun*, 2020, 527(3): 611–617
- [38] WU P K, HONG S K, CHEN W, et al. Mortalin (HSPA9) facilitates BRAF-mutant tumor cell survival by suppressing ANT3-mediated mitochondrial membrane permeability[J]. *Sci Signal*, 2020, 13(622): eaay1478
- [39] HAO Y, YE M, CHEN X, et al. Discovery and validation of FBLN1 and ANT3 as potential biomarkers for early detection of cervical cancer[J]. *Cancer Cell Int*, 2021, 21(1): 125
- [40] GALLERNE C, TOUAT Z, CHEN Z X, et al. The fourth isoform of the adenine nucleotide translocator inhibits mitochondrial apoptosis in cancer cells[J]. *Int J Biochem Cell Biol*, 2010, 42(5): 623–629
- [41] GONG K, TAN Z, LIU H, et al. A novel mutation of glycogen synthase kinase -3 β leads to a reduced level of GSK3 β protein in a patient with dilated cardiomyopathy[J]. *Genes Dis*, 2024, 11(1): 84–86
- [42] CHEN L, FU G, JIANG C. Deep learning-derived 12-lead electrocardiogram-based genotype prediction for hypertrophic cardiomyopathy: a pilot study[J]. *Ann Med*, 2023, 55(1): 2235564
- [43] STARR N, IOANNOU A, MARTINEZ - NAHARRO A. Monitoring cardiac amyloidosis with multimodality imaging[J]. *Rev Esp Cardiol(Engl Ed)*, 2024, 77(1): 79–87
- [44] TABIRA A, MISUMI I, SATO K, et al. Mid-ventricular obstructive cardiomyopathy after takotsubo cardiomyopathy[J]. *Intern Med Tokyo Jpn*, 2023, 62(16): 2365–2373
- [45] 黄娟, 郭晓峰, 吉炜. 致心律失常性右室心肌病患者1例的PKP2基因变异分析[J]. *中华医学遗传学杂志*, 2023, 40(9): 1165–1170
- [46] MARON B J, TOWBIN J A, THIENE G, et al. Contemporary definitions and classification of the cardiomyopathies[J]. *Circulation*, 2006, 113(14): 1807–1816
- [47] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990 - 2015: a systematic analysis for the Global Burden of Disease Study 2015[J]. *Lancet*, 2016, 388(10053): 1545–1602
- [48] SCHULTHEISS H P, SCHULZE K, DÖRNER A. Significance of the adenine nucleotide translocator in the pathogenesis of viral heart disease[J]. *Mol Cell Biochem*, 1996, 163/164: 319–327
- [49] SCHAEFER P M, HUANG J, BUTIC A, et al. Nicotinamide riboside alleviates exercise intolerance in ANT1-deficient mice[J]. *Mol Metab*, 2022, 64: 101560
- [50] PORTMAN M A. Adenine nucleotide translocator in heart[J]. *Mol Genet Metab*, 2000, 71(1/2): 445–450
- [51] WINTER J, KLUMPE I, HEGER J, et al. Adenine nucleotide translocase 1 overexpression protects cardiomyocytes against hypoxia via increased ERK1/2 and AKT activation[J]. *Cell Signal*, 2016, 28(1): 152–159
- [52] ESPOSITO L A, MELOV S, PANOVA, et al. Mitochondrial disease in mouse results in increased oxidative stress[J]. *Proc Natl Acad Sci USA*, 1999, 96(9): 4820–4825
- [53] PARODI-RULLÁN R M, CHAPA-DUBOCQ X, GUZMÁN-HERNÁNDEZ R, et al. The role of adenine nucleotide translocase in the assembly of respiratory super complexes (下转第566页)

- 2018, 11: 57–66
- [33] CHENG Y, RONG J. Pro - resolving lipid mediators as therapeutic leads for cardiovascular diseases [J]. *Expert Opin Ther Targets*, 2019, 23(5): 423–436
- [34] GIL - VILLA A M, ALVAREZ A M, VELÁSQUEZ - BERRÍO M, et al. Role of aspirin-triggered lipoxin A4, aspirin, and salicylic acid in the modulation of the oxidative and inflammatory responses induced by plasma from women with pre-eclampsia [J]. *Am J Reprod Immunol*, 2020, 83(2): e13207
- [35] DE MATTEIS R, FLAK M B, GONZALEZ-NUNEZ M, et al. Aspirin activates resolution pathways to reprogram T cell and macrophage responses in colitis - associated colorectal cancer [J]. *Sci Adv*, 2022, 8(5): eabl5420
- [36] SIMÕES R L, FIERRO I M. Involvement of the Rho-kinase/myosin light chain kinase pathway on human monocyte chemotaxis induced by ATL-1, an aspirin-triggered lipoxin A4 synthetic analog [J]. *J Immunol*, 2005, 175(3): 1843–1850
- [37] PRIETO P, ROSALES-MENDOZA C E, TERRÓN V, et al. Activation of autophagy in macrophages by pro-resolving lipid mediators [J]. *Autophagy*, 2015, 11(10): 1729–1744
- [38] O'SULLIVAN T P, VALLIN K S A, ALI SHAH S T, et al. Aromatic lipoxin A4 and lipoxin B4 analogues display potent biological activities [J]. *J Med Chem*, 2007, 50(24): 5894–5902
- [39] BÖRGESON E, JOHNSON A M F, LEE Y S, et al. Lipoxin A4 attenuates obesity-induced adipose inflammation and associated liver and kidney disease [J]. *Cell Metab*, 2015, 22(1): 125–137
- [40] DONG T, DAVE P, YOO E, et al. NAP1051, a lipoxin A4 biomimetic analogue, demonstrates antitumor activity against the tumor microenvironment [J]. *Mol Cancer Ther*, 2021, 20(12): 2384–2397
- [41] 郭琪琪. BML-111 通过抑制 P2X7 受体减少 M1 型小胶质细胞/巨噬细胞减轻实验性大鼠脑梗死 [D]. 遵义: 遵义医科大学, 2020
- [42] CAO E, XU J, GONG Y, et al. Effect of the lipoxin receptor agonist BML-111 on cigarette smoke extract-induced macrophage polarization and inflammation in RAW264.7 cells [J]. *Int J Chron Obstruct Pulmon Dis*, 2023, 18: 919–932
- [43] WU B, WALKER J A, TEMMERMAND D, et al. Lipoxin a(4) promotes more complete inflammation resolution in sepsis compared to stable lipoxin a(4) analog [J]. *Prostaglandins Leukot Essent Fatty Acids*, 2013, 89(1): 47–53

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(本文编辑: 蒋 莉)

(上接第 552 页)

- in cardiac cells [J]. *Cells*, 2019, 8(10): E1247
- [54] SARMA U, RIPKA L, ANYAEGBUNAM U A, et al. Modeling cellular signaling variability based on single-cell data: the TGFβ-SMAD signaling pathway [J]. *Methods Mol Biol*, 2023, 2634: 215–251
- [55] HEGER J, ABDALLAH Y, SHAHZAD T, et al. Transgenic overexpression of the adenine nucleotide translocase 1 protects cardiomyocytes against TGFβ1-induced apoptosis by stabilization of the mitochondrial permeability transition pore [J]. *J Mol Cell Cardiol*, 2012, 53(1): 73–81

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