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TFEB与线粒体稳态在脓毒症并发症中的调控机制

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摘要 脓毒症是由宿主感染引起的炎症反应综合征, 伴随着多器官功能障碍, 对心血管系统的影响尤为显著. 脓毒症患者心肌功能障碍包括炎症、线粒体功能紊乱、氧化应激、低代谢等. 线粒体稳态是维持机体健康的重要基础, 线粒体功能障碍会引发心肌炎症甚至心力衰竭. 转录因子EB(transcription factor EB, TFEB)是调控自噬和溶酶体生物发生的关键转录因子, 在线粒体自噬和线粒体生物发生, 以及心血管的稳态调控中发挥至关重要的作用. 本文总结了近年来脓毒症中TFEB与线粒体调控和功能的研究进展, 并讨论了TFEB在细胞内稳态和脓毒症并发症中的潜在作用.

关键词 TFEB, 线粒体, 自噬, 心血管损伤, 脓毒症, 炎症

脓毒症是由宿主感染引起的炎症反应综合征, 是重症监护病房患者预后不良的主要原因. 脓毒症患者主要死于多器官功能障碍[1]. 其中心脏是脓毒症最易影响的器官, 近40%~50%的脓毒症患者都存在心肌功能障碍[2]. 炎症常伴有活性氧(reactive oxygen species, ROS)形成导致的氧化应激. 同时, 氧化应激还通过激活促炎进一步破坏线粒体, 引发脓毒症患者器官功能障碍. 消除损伤的线粒体和线粒体生物发生过程之间的平衡可能会在器官功能障碍当中发挥重要作用[3]. 因此, 抑制或减轻氧化应激反应可能是预防脓毒症发生的潜在措施.

自噬与脓毒症密切相关. 败血症模型中自噬的完全激活有利于心脏的保护[4]. 自噬也是心血管氧化还原稳态的调节因子, 氧化应激、自噬和炎症相互作用对维持心血管稳态和功能至关重要[5,6]. 虽然人们认为自噬主要是一种有益的适应机制, 但在一些情况下过度自噬与心脏病理学有关[7]. 转录因子EB(transcription factor EB, TFEB)被确定为溶酶体生物发生和自噬的主要调节剂[8], 参与溶酶体到细胞核的信号转导, 调控涉及溶酶体生物发生、自噬和溶酶体胞吐等多种过程的基因转录[9,10], 并与细胞代谢密切相关[8]. 研究表明, TFEB通过增强溶酶体功能和减少促炎细胞因子分泌(如白细胞介素-1β), 从而抵抗动脉粥样硬化的发生和发展[9]. TFEB增加自噬相关基因在内皮细胞(endothelial cells, ECs)中的表达, 促进血管生成和心肌梗死后心脏功能的恢复[11]. TFEB的下调会导致自噬通量受

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损、心肌氧化应激的增加[12,13]. 因此, TFEB介导的自噬和溶酶体生物发生的调控可能对治疗心血管炎症性疾病有益.

脓毒症期间会发生生物能量改变, 包括低代谢和自噬异常[3]. 线粒体损伤是心肌细胞存活率下降的重要因素. 细胞通过自噬清除受损或功能异常的线粒体, 这一过程可能是细胞处于低代谢状态的部分原因, 但是这种低代谢状态又被细胞生成的新线粒体即线粒体生物发生而抵消[3,13]. 线粒体大约占心肌体积的三分之一, 线粒体自噬是细胞选择性清除受损或者多余线粒体的自噬溶酶体途径, 它是线粒体应激反应及线粒体稳态调节的重要组成部分[14], 线粒体自噬对健康和疾病中的心血管稳态尤为重要[5,15]. 许多研究发现, TFEB在调控细胞内线粒体稳态发挥了重要作用, 在脓毒症并发症以及其他疾病中的临床意义不可忽视, 本文就此展开综述和讨论.

1　TFEB活化机制

TFEB是MiTF/TFE(microphthalmia-associated transcription factor/transcription factor E)家族成员, 由476个氨基酸残基组成, 主要模序为富谷氨酰胺(glutamine, Gln)区域、螺旋-环-螺旋(basic-helix-loop-helix, bHLH)结构域、亮氨酸拉链(leucine zipper, LZ)结构、富脯氨酸(proline, Pro)区域[16]. TFEB作为调控自噬、细胞代谢等细胞重要生理过程的转录因子, 其活性的调节对细胞的生理状态和疾病的治疗具有重要意义.

TFEB的转录活性取决于其亚细胞定位, 而其亚细胞定位主要由Ser142和Ser211的磷酸化状态所决定, 通常TFEB去磷酸化后才可进入核内发挥转录活性[17]. 静息态的细胞在营养充足的条件下, 雷帕霉素激酶的机制靶点(mammalian target of rapamycin, mTOR)和丝裂原活化蛋白激酶1(mitogen activated protein kinase 1, MAPK1)在Ser142和Ser211磷酸化TFEB, 以增强其与细胞质伴侣酪氨酸3-单加氧酶/色氨酸5-单加氧酶活化蛋白(tyrosine 3-monooxygenase/tryptophan 5-monooxygenase, YWHA/14-3-3)的结合, 导致TFEB被滞留在细胞质中, 降低了TFEB的转录活性[18]. 而细胞在处于饥饿或者溶酶体功能障碍的状态时, 溶酶体释放Ca^{2+}激活磷酸酶、钙调磷酸酶, 在Ser142和Ser211去磷酸化TFEB, 促进TFEB核易位, 激活下游基因转录[19], 发挥生物学功能. 图1展示了TFEB蛋白基本结构图及影响其转录活性的重要位点.

2　TFEB与线粒体调控关系

线粒体是有氧代谢的主要场所, 可通过一系列氧化磷酸化作用生成ATP, 为机体提供90%以上的能量供给. 同时, 线粒体也是细胞内物质代谢、天然免疫以及细胞死亡的调控中心, 因此线粒体的质量需要被严密调控. 线粒体的质量调控指衰老或损伤的线粒体被清除以及新的线粒体产生的过程. 细胞通过自噬清除衰老和损伤的细胞器, 这一过程叫做线粒体自噬, 线粒体的数量增加依赖于线粒体生物发生产生新的线粒体, 而线粒体发生主要是由一系列转录因子及转录共激活因子调控的[20]. 线粒体的功能异常与多种疾病密切相关, 在正常情况下, 机体的组织器官内线粒体都保持在一个稳定状态, 因此对于线粒体自噬与线粒体生物发生协同调控线粒体的研究具有重要意义. TFEB不仅是溶酶体和自噬体生物发生的主要调节因子[8], 同时还参与了线粒体内稳态调控. 最新研究发现, 受损线粒体释放信号启动TFEB/HLH-30向细胞核的转运, 激活溶酶体的生物发生和自噬, 以阻止线粒体的氧化应激对细胞稳态的影响[21]. 这也为进一步研究TFEB与受损线粒体的关系提供了理论依据. 越来越多的研究表明, TFEB可以维持线粒体自噬和线粒体生物发生之间的平衡[22].

2.1　TFEB与线粒体自噬

线粒体作为ATP的主要来源, 在启动程序性细胞死亡以及多种细胞内过程中发挥重要作用[23]. 然而线粒体对氧化应激非常敏感, 易受到损伤. 当线粒体受损伤时, 大量的氧化酶释放出来[24]; 过多的氧化酶释放会导致更严重的氧化应激和线粒体损伤, 从而引起线粒体的自噬, 线粒体自噬在正常的细胞器更替、细胞成熟和线粒体损伤清除过程中起作用, 更是一种自我保护机制[25,26]. 缺乏自噬会促进炎症反应和氧化应激, 最终导致不同组织的各种病理疾病[27,28]. 注射脂多糖(lipopolysaccharide, LPS)是建立体内脓毒症动物模型的常用方法. 研究表明, 在脂多糖诱导的急性肺

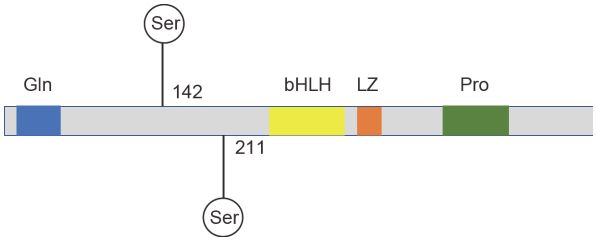

图 1 TFEB蛋白基本结构图及影响其转录活性的重要位点. Ser: 丝氨酸; Ser142: 丝氨酸142磷酸化位点; Ser211: 丝氨酸211磷酸化位点; Gln: 富谷氨酰胺区域; bHLH: 螺旋-环螺旋结构域; LZ: 亮氨酸拉链结构; Pro: 富含脯氨酸区域

Figure 1 Basic structure of the TFEB protein and the key sites that affect its transcriptional activity. Ser: Serine; Ser142: phosphorylation site at Ser142; Ser211: phosphorylation site at Ser211; Gln: glutamine rich region; bHLH: basic-helix-loop-helix domain; LZ: leucine zipper region; Pro: proline rich region

损伤模型中, TFEB可通过上调自噬相关蛋白的表达激活线粒体自噬, 由于线粒体受损会释放ROS, ROS通过瞬时受体电位阳离子通道(mucolipin subfamily, TRPML1)释放钙介导TFEB的核定位从而促进自噬[23,29], 以减少LPS诱导的炎症和线粒体损伤[30]. 自噬是细胞生存和稳态的重要调节因子, 但过度的自噬往往会引发更严重的炎症反应、多器官衰竭甚至是机体死亡. 研究已经发现线粒体过度自噬带来的损伤与炎症小体的激活有关. 在脓毒症中, 线粒体自噬被广泛激活以清除受损的线粒体以防止进一步的器官损伤, 而受损的线粒体自噬导致NLRP3(NLR家族含有3个pyrin结构域的炎症小体)的过度激活, 并增加脓毒症动物的死亡率[31]. 最近研究发现, 当锰导致TFEB的核定位下降时, 小鼠纹状体星形胶质细胞自噬功能会出现障碍, 从而抑制线粒体的自噬溶酶体降解, 使线粒体损伤积累[32]. 然而TFEB过表达可逆转自噬功能障碍和线粒体损伤积累. 并且最近发现, 木犀草素可通过上调TFEB的表达来促进线粒体自噬减轻阿霉素诱导的心脏毒性[33]. 进一步研究发现, TFEB促进自噬完成线粒体清除后, 促进了线粒体生物发生来合成新的线粒体抵抗LPS/D-galactosamine(D-GalN)诱导的肝炎[23]. 因此, TFEB在控制线粒体自噬和生物发生动态平衡以恢复正常的线粒体膜电位中发挥重要作用[34]. 此外, 通过TFEB介导的自噬和溶酶体生物发生的调控可能为炎症疾病以及心血管疾病的治疗提供新的思路, 从而帮助人们找到更有效的办法来减缓脓毒症等带来的心脏功能的损伤.

2.2 TFEB与线粒体生物发生

线粒体生物发生是产生新的线粒体的过程, 会因细胞应激或对环境的变化做出反应时被多种不同信号因子激活, 从而得到较高的线粒体拷贝数来保护细胞[20]. 这也是脓毒症患者的一种保护反应, 可以在减少线粒体损伤的同时降低炎症反应, 既保证了线粒体数目又不会因机体产生过度的线粒体自噬而死亡. 线粒体生物发生受到几个关键转录因子的严格调控. 最近研究表明, 运动通过AMPK-SIRT1-TFEB通路激活自噬溶酶体功能, 同时三羧酸循环的中间产物NAD^+也可以激活SIRT1[35], 进而激活线粒体生物发生, 改善细胞状态. Sirtuin蛋白1(Sirtuin 1, SIRT1)是一种来自Sirtuin家族的蛋白质, 为NAD^+依赖的去乙酰化酶, NAD^+可激活SIRT1, 降低氧化应激, 增强脱乙酰作用, 提高过氧化物酶体增殖激活受体-γ共激活因子-1α(peroxisome proliferator-activated receptor-γ coactivator 1 α, PGC-1α)水平从而激活线粒体生物发生[36]. 研究已经证实, 在此途径中TFEB直接调节PGC-1α表达, PGC-1α通过控制能量代谢调节线粒体生物发生[37]. 同样地, 在肝损伤模型中, TFEB激活溶酶体生物发生完成于线粒体清除后, 上调PGC-1α启动了线粒体生物发生从而实现线粒体的更新[22]. 但是也有研究表明, TFEB可以独立于PGC-1α调控骨骼肌线粒体的生物发生和葡萄糖摄取[38], 并且这一过程没有激活自噬通路. 这些发现表明, TFEB并不完全依赖于PGC-1α的存在以诱导线粒体生物发生, 在不同的组织、细胞内, TFEB激活通路也各有差异. 核因子/类红血球2(nuclear factor erythroid-2-related factor 2, NFE2L2/NRF2)是一种可被TFEB激活的核转录因子[39], 被TFEB激活后可通过抗氧化反应元件控制多种解毒酶的表达, 促进线粒体生物发生并减轻细胞毒害损伤. 除TFEB外, SQSTM1/p62也可通过促进AMP活化蛋白激酶(adenosine 5′-monophosphate (AMP)-activated protein kinase, AMPK)AMPK和Unc-51样自噬激活激酶(unc-51 like autophagy activating kinase 1, ULK1)之间的相互作用, 诱导ULK1磷酸化, 导致巨噬细胞自噬/自噬诱导, 使得NFE2L2被活化[40], 进而同样起到解毒作用. 最新研究发现, AMPK-SIRT1-PGC-1α-NFE2L2信号通路介导了烧伤诱导的心脏功能障碍和心脏线粒体损伤[41]. 由此可见, TFEB与NFE2L2在线粒体生物发生发挥重要作

用, 虽然还有很多潜在机制有待研究, 但其无疑与心脏功能障碍及炎症等疾病有着密不可分的联系. 彻底弄清线粒体生物发生机制及其中关键调节因子TFEB的调节机制将为未来心肌损伤等多种相关疾病的诊疗提供新的药物研究靶点及现实依据.

在脓毒症患者中, 随着病情加重, 机体耗氧量逐渐减少, 组织内氧含量反而升高, 同时出现线粒体功能及数量的变化, 提示线粒体稳态变化的失衡可能是脓毒症病理生理作用的亚细胞靶点[42]. 因此, 线粒体稳态的调控对治疗脓毒症至关重要. 通过以上机制, TFEB可调控线粒体自噬与线粒体生物发生(图2), 但是仍有很多机制尚未研究清楚, 需进一步探究.

3　脓毒症与心血管损伤

脓毒症会影响微循环, 引起脓毒性心肌病, 导致持续性低血压等心血管并发症[43]. 而脓毒症患者一旦发生心血管并发症, 其死亡概率可能高达70%甚至更高[44]. 因此, 对脓毒症中心血管并发症的研究至关重要.

3.1　线粒体自噬在脓毒症心血管损伤中的作用

线粒体在心肌细胞中高度表达, 主要通过氧化磷酸化过程产生能量, 在维持细胞动态平衡和细胞存活中发挥重要作用. 已有研究报道, 线粒体网络受损和线粒体异常积累是导致各种心脏病和心力衰竭的重要发病机制[45,46]. 线粒体呼吸和氧化磷酸化的损坏可引起ROS生成和线粒体DNA(mitochondrial DNA, mtDNA)重排的增加, 导致细胞凋亡、炎症, 加速衰老和细胞死亡, 促进心血管损伤[47,48]. 线粒体自噬与脓毒症引起的炎症反应密切相关[49]. 当机体出现脓毒症状时, 早期阶段会增加人体内的心、脑、肝、肾等各个

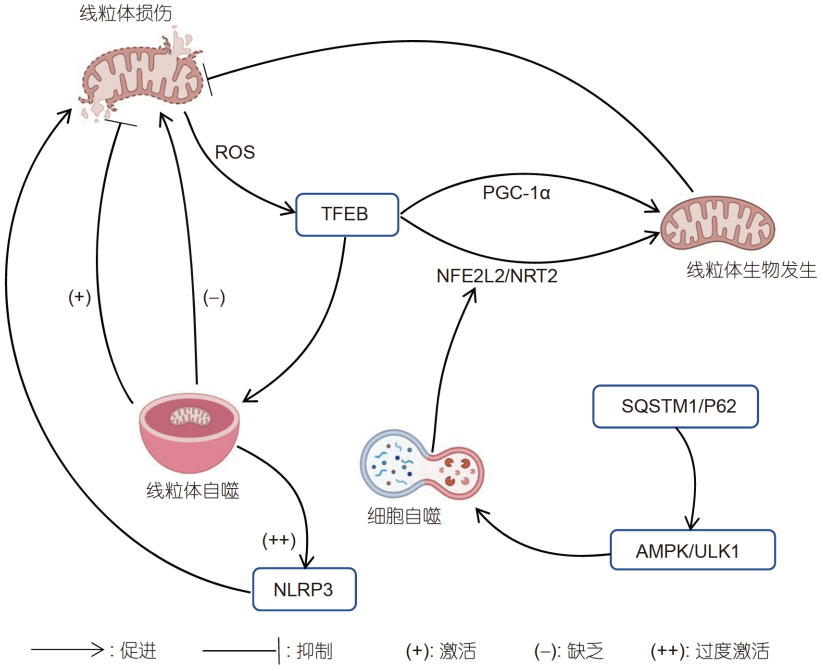

图 2　TFEB与线粒体自噬和线粒体生物发生之间的关系. 线粒体损伤导致ROS积累, 促进TFEB核易位. TFEB通过直接增强PGC-1α的表达, 激活*NFE2L2*/*NRT2*等自噬相关基因促进线粒体生物发生或直接促进线粒体自噬来减轻线粒体损伤. 线粒体自噬缺乏, 或由于线粒体自噬过度从而产生炎症小体都会加重线粒体损伤. 除TFEB外, SQSTM1/P62也可通过促进AMPK和ULK1相互作用来促进细胞自噬, 激活*NFE2L2*/*NRT2*, 促进线粒体生物发生, 减轻线粒体损伤

Figure 2　Relationship between TFEB and mitochondrial autophagy (mitophagy) and mitochondrial biogenesis. Mitochondrial damage leads to the accumulation of ROS and promotes the nuclear translocation of TFEB. TFEB directly enhances the expression of PGC-1α, activates autophagy-related genes, such as *NFE2L2*/*NRT2*, to promote mitochondrial biogenesis, or directly promotes mitophagy to reduce mitochondrial damage. Mitophagy deficiency, or the excessive mitophagy-induced production of inflammasomes, can aggravate mitochondrial damage. In addition to TFEB, SQSTM1/P62 can also promote autophagy by promoting the interaction between AMPK and ULK1, activate *NFE2L2*/*NRT2*, facilitate mitochondrial biogenesis, and reduce mitochondrial damage

重要部位的细胞自噬活力, 通过降低炎症因子释放, 调节免疫反应, 清除被破坏的线粒体维持人体内的脂质代谢平衡, 从而发挥对机体的保护作用. 但随着脓毒症进展, 自噬水平过度增高会对免疫细胞造成损害[50]. 目前, 已经确定线粒体自噬受E3泛素连接酶Parkin与线粒体丝氨酸-苏氨酸激酶PTEN诱导的推定激酶1 (PTEN induced putative kinase 1, PINK1)[51]以及非PINK1-Parkin途径调控. 已有相关研究表明, 对线粒体自噬的调控可改善脓毒症所引起的心脏功能障碍与炎症反应. 例如, 在脓毒症中, Beclin-1通过PINK1-Parkin促进线粒体自噬, 改善心脏功能, 减轻炎症[52]. 美洲大蠊提取物心脉隆(XML)通过PINK1/Parkin途径介导线粒体自噬, 从而调节脓毒症诱导的心肌细胞损伤[53]. 且TSG101可提高PINK1/Parkin途径介导的线粒体自噬, 改善小鼠心肌收缩能力, 减少炎症因子[51]. 米诺环素通过Akt/mTOR信号传导促进心肌细胞线粒体自噬以改善脓毒症诱导的心脏功能障碍[54]. 线粒体自噬除了能改善心脏功能还能改善其他器官的功能状态. 例如, 在脓毒症急性肝损伤中, 吸入抗氧化氢后, 小鼠肝组织FUNDC1蛋白表达水平低于模型组, 而p62和LC3B-Ⅱ蛋白表达水平明显升高, 加速了线粒体自噬过程, 有效提高了小鼠生存率[55]. 脓毒症急性肾损伤时, 线粒体中瞬时受体电位锚蛋白1可增强BNIP3蛋白表达, 引起血清尿素和肌酐水平下降, 保护肾功能[56]. 综上所述, 线粒体自噬对心、肝、肾等器官都具有保护作用, 尤其是对心脏功能障碍的保护作用. 对线粒体自噬的调控有助于改善脓毒症的预后. 这为治疗脓毒症心血管并发症提供了研究方向.

3.2 TFEB在脓毒症心血管并发症中的作用

TFEB是自噬过程中关键的转录因子, 可直接调控自噬相关基因, 如*LC3*和*Beclin1*等[8,10]. 在哺乳动物体内, TFEB去磷酸化后, 核易位激活自噬信号通路, 包括自噬体形成, 随后自噬体与溶酶体融合, 从而发挥降解作用. 降解后所产生的大分子被释放到细胞质中重新利用, 使细胞不断适应不同的营养环境和维持细胞内环境的稳定[57]. 在脓毒症中, Toll样受体4(Toll-like receptor 4, TLR4)发挥对炎症的识别和调节作用[58], 小胶质细胞的自噬依赖于上游调节因子TLR4[59]. 在炎性反应中, 激活的B细胞核因子Kappa-轻链增强子(nuclear factor-kappa B, NF-κB)对炎症基因起着重要调控作用. 布托啡诺可通过调控NF-κB通路, 降低血清炎症因子TNF-α, IL-6和IL-1的表达水平, 减轻脓毒症大鼠的炎症反应[60]. 在LPS模型中LR4/CD14复合物由心肌细胞表达, 通过直接作用于心肌细胞而降低心肌细胞收缩力, 并诱导NF-κB的激活, 控制*IL-1*, *IL-6*和*IL-8*基因表达上调, 导致免疫降低[30]. TFEB上调降低了IL-1和IL-6等炎性因子的表达, 增高了自噬相关基因表达, 促进线粒体自噬, 从而减少LPS诱导的肺组织和肺泡上皮细胞的炎症和线粒体损伤[61]. TFEB/NF-κB介导的信号通路具有治疗心脏毒性的作用[62]. 在脓毒症模型中, TFEB还可通过提高自噬水平来减轻心肌损伤[63], 褪黑激素可显著改善心肌功能障碍, 减少炎症细胞因子的释放, 激活AMPK, 改善线粒体功能, 激活自噬[64]; AMPK-TFEB信号通路可调控自噬[65], 通过清除过量的ROS改善心肌损伤[66,67]. 因此, TFEB可能通过调节自噬或者TFEB/NF-κB信号通路改善LPS导致的心脏功能障碍. 本课题组在LPS体外实验中发现, TFEB过表达通过溶酶体自噬途径改善了LPS诱导的线粒体功能失调, 降低了ROS水平, 从而抑制了心肌细胞炎性损伤. 综上研究表明, TFEB可通过调节自噬和线粒体功能来调节脓毒症所引起的心血管并发症, 揭示了TFEB和自噬在脓毒症中的重要作用.

4 TFEB在其他病理生理中的调控作用

4.1 清除作用

自噬是一种自我保护机制, 能够降解和清除人体中受损害的细胞器官或者异常的蛋白质及其脂质. 自噬失调与各种疾病密切相关, 包括心脏疾病、神经退行性疾病、癌症、免疫性疾病等[68]. TFEB可与众多自噬基因的启动子区域结合, 并诱导自噬体生物发生和自噬体溶酶体融合. 例如, TFEB介导的溶酶体重塑通过提高自噬体溶酶结合(autophagy lysosomal pathway, ALP)活性来防止心肌损伤[69], 这为治疗脓毒症引起的心肌损伤提供了新思路. 溶酶体是主要参与降解和再循环过程的囊泡状细胞器, TFEB通过激活溶酶体Ca^{2+}离子通道MCOLN1, 诱导溶酶体胞吐[70]. 研究表明, TFEB促进胞吐基因的表达[71], 并在饥饿条件下增加细胞内吞率, 诱导胞吐作用, 促进细胞自噬[72,73]. 无论是TFEB促进ALP活性还是诱导胞吐都为治疗脓毒症并发症提供了新的研究方向与治疗策略.

4.2　介导炎症

TFEB可通过直接机制调节先天免疫和炎症, 控制炎症介质的转录, 并通过间接机制控制影响微生物感染、机体代谢和系统炎症信号的细胞过程. 研究人员在小鼠膀胱内注入针对三种不同蛋白酶激活受体(protease activated receptors, PARs)的肽激动剂, 将其作为膀胱炎的模型, 利用包含345个不同TFEB共有序列的蛋白质DNA微阵列技术, 从膀胱黏膜炎核提取物中鉴定出唯一激活的转录因子是TFEB, 首次提出了TFEB表达与炎症的相关性[74]. 进一步研究发现, TFEB是一种进化保守的宿主防御转录因子, 直接控制IL-6和TNF-α分泌以抵抗感染[75~77]. TFEB可以直接调控炎症, 根据组织和环境发挥促炎或抗炎作用, 对脓毒症并发症有一定的治疗意义. TFEB和TFE3在巨噬细胞可激活先天免疫系统, 提高杀菌功能, 产生各种细胞因子和趋化因子[78]. TFEB和TFE3可能存在多种活化模式, 通过调节溶酶体和自噬在炎症信号通路中发挥更广泛的作用[79]. 因此, TFEB信号通路的作用仍存在争议. 这促使人们进一步探究在体和体外TFEB及相关信号通路的作用.

4.3　控制代谢

近两年最新研究表明, TFEB及其调控的下游通路在细胞代谢中发挥着越来越重要的作用. 脂代谢和免疫系统之间存在重要的生理平衡关系, 二者任一方的异常都会影响彼此系统的正常工作[80]. 研究证明, 在脓毒症患者中会出现多器官受损, 免疫功能、糖脂代谢以及线粒体功能失调, ATP产能降低, 胆固醇等脂蛋白表达异常等[81,82]. 而TFEB核易位可通过调节PGC1-α和PPARα激活脂代谢, 促进线粒体功能[83]. 在饥饿环境下, TFEB可促进脂肪酸分解代谢、脂肪酸氧化和生酮作用, 同时抑制高脂饮食喂养小鼠的肥胖和代谢综合征的发生[84]. 在大鼠的肝脏内, TFEB过表达可提高脂肪代谢, 而缺乏TFEB的小鼠, 体内自噬不足导致脂肪堆积[83]. 随着脓毒症研究的逐渐深入, 脓毒症患者体内免疫细胞的代谢调节, 以及炎性反应与代谢的关系已受到越来越多的关注[85]. TFEB或许可通过改善代谢异常从而对脓毒症起到治疗作用.

5　总结与展望

近期TFEB的研究得到了广泛关注. 作为一种至关重要的转录因子, TFEB在心血管疾病、溶酶体贮积症、炎症、肿瘤、代谢综合征等相关疾病中都发挥着不可或缺的作用. TFEB可通过上调自噬改善心脏功能障碍, 因此, 对心血管疾病具有潜在的治疗意义. 例如, 在阿霉素诱导的心脏毒性的治疗中, mTOR-TFEB-IKK信号传导途径可以抑制NF-κB介导的炎症[62]. 在缺血的血管中, TFEB通过激活AMPKα和自噬而成为血管生成的正调节剂[86]. 在巨噬细胞中的TFEB可独立于ATG5介导的自噬减轻心肌梗死后的心室功能障碍[87].

脓毒症所引起的心肌损伤严重影响脓毒症患者的预后, 但是关于脓毒症心肌损伤的相互作用机制尚未研究透彻. 已有研究表明, TFEB的上调降低了炎性因子的表达, 同时升高了自噬相关基因的表达, 从而促进线粒体自噬, 减少了LPS诱导的肺组织和肺泡上皮细胞的炎症和线粒体损伤[61]. 虽然TFEB对线粒体稳态的调控给人们带来了新的研究思路. 但是目前对TFEB调控线粒体稳态在生理或者病理情况下的功能的认识还远远不足, 仍然需要不断深入探索, 从而为相关疾病的治疗提供新的方向和依据. 在未来的深入研究中TFEB可成为多种疾病的分子靶标.

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Regulation of TFEB and mitochondrial homeostasis during sepsis complications

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Sepsis is an inflammatory response syndrome caused by host infection. It is accompanied by multiple organ dysfunction, which has a significant impact on the cardiovascular system. Myocardial dysfunction in patients with sepsis includes inflammation, mitochondrial disorder, oxidative stress, and low metabolism. Mitochondrial dysfunction can cause myocardial inflammation and even heart failure. Transcription factor EB (TFEB), a transcription factor that regulates autophagy and lysosomal biogenesis, acts as an important regulator for maintaining cardiovascular homeostasis. It plays an essential role in the regulation of mitochondrial biogenesis and mitophagy to maintain cellular homeostasis. In this article, we summarize the recent research progress made in understanding TFEB and its role in regulating mitochondrial function in sepsis. We also discuss the potential role of TFEB in cellular homeostasis during septic complications.

TFEB, mitochondrion, autophagy, cardiovascular injury, sepsis, inflammation

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