oxygenase-1,HO-1)通路抑制铁死亡来缓解脓毒症诱导的 ALI 中的肺泡上皮屏障功能障碍[3]。目前研究的热点分子富含 AU 元件的 RNA 结合因子 1(AU-rich element-RNA binding factor 1,AUF1)不仅可抑制炎症反应和减轻脓毒症相关症状[27],还可通过正向调节 Nrf2 和负向调节激活转录因子 3(activation transcription factor 3,ATF3)抑制肺泡上皮细胞铁死亡来减轻脓毒症 ALI[28]。PCTR1(protectin conjugates in tissue regeneration 1)是保护素家族的成员,是一种特异性的消炎调节剂,可促进炎症消退,加速组织修复[29],同样有研究表明 PCTR1 可能通过激活 ALX(lipoxin A4)/蛋白激酶 A(protein kinase A,PKA)/cAMP 反应元件结合蛋白(cyclic-AMP response binding protein,CREB)通路抑制 ALI 中肺上皮细胞的铁死亡[30]。上述研究提示,以肺上皮细胞铁死亡通路为调节靶点,有可能成为控制脓毒症 ALI 发生及发展的有效治疗途径。

2.3 抑制巨噬细胞铁死亡

巨噬细胞是肺部最主要的免疫细胞之一,在脓毒症 ALI 中起着至关重要的作用。脓毒症模型中巨噬细胞被募集和活化释放促炎细胞因子,并同时诱导中性粒细胞浸润,进一步加重炎症、破坏内皮屏障、阻塞肺微循环,加剧肺损伤[31]。衣康酸是近年来在巨噬细胞中发现的具有显著抗炎活性的小分子代谢物,已被证实广泛参与免疫调节、氧化应激和脂质过氧化过程。较新的研究也表明衣康酸还可通过 Nrf2 途径抑制巨噬细胞铁死亡改善脓毒症 ALI[32]。尿苷是一种嘧啶核苷,是人体血液中含量最丰富的核苷,近些年研究报道了其抗炎[33]、抗纤维化[34]、抗氧化[35]和抗衰老[36]的功能。研究还报道了尿苷可通过激活 Nrf2 通路和抑制 ACSL4 表达从而抑制巨噬细胞铁死亡改善脓毒症 ALI[37]。H_2S 是一种生理气体可自由穿过细胞膜,其作为信号分子独立于任何特定的转运蛋白起作用。有研究称 H_2S 可调节微生物的各种生理功能,包括炎症、线粒体功能、氧化应激、内质网应激、神经保护和血管舒张等[38]。在铁死亡相关研究中 H_2S 通过阻断哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)信号传导抑制巨噬细胞铁死亡并刺激细胞自噬减弱脓毒症 ALI[39]。因此抑制巨噬细胞铁死亡或将成为调节脓毒症 ALI 新的治疗靶点。

目前已证实脓毒症 ALI 的发生与多种细胞的铁死亡密切相关,以上皮细胞、微血管内皮细胞及巨噬细胞的破坏最为常见(表 1),抑制铁死亡的治疗方法在脓毒症 ALI 的治疗中发挥潜在作用。

3 细胞死亡之间的串扰

细胞死亡分坏死和程序性细胞死亡。坏死是一种非程序性细胞死亡形式,通常由创伤性损伤引起;程序性细胞死亡是一种受基因调控的细胞死亡,其不仅对机体的生长发育及组织器官的稳态具有重要作用,还参与了多种病理过程。长久以来,各种细胞死亡途径一直被认为是并行运作几无重叠的,然而目前越来越多的证据强调它们之间存在广泛的串扰,并且可以相互交叉调节[40]。

新的细胞死亡形式不断被发现,凋亡、焦亡、坏死性凋亡、自噬、铁死亡、铜死亡、泛凋亡等[41]。随着泛凋亡被报道,细胞死亡之间的串扰机制也相应被不断揭开[42]。泛凋亡是一种炎症性程序细胞死亡,受到泛凋亡小体复合物的调控,具有细胞焦亡、凋亡和(或)坏死性凋亡的关键特征,且不被其中任意一种死亡方式单独表征[43]。细胞凋亡、自噬和铁死亡以 ROS 介导的脂质过氧化为中枢环节相互串扰影响疾病发生发展[44]。在二氧化硅诱导的矽肺纤维化病理过程中,细胞自噬、凋亡和焦亡相互串扰,Bcl-2 蛋白、NLRP3 炎症小体或是其发生串扰的关键分子[45]。铁和铜作为人体重要的微量元素,他们对于维持身体机能至关重要,在慢性肾病的研究中,铁死亡和铜死亡或可通过 ROS 的积累导致线粒体损伤发生相互串扰导致疾病进展[46]。在急性呼吸窘迫综合征(ARDS)疾病过程中,铁死亡、焦亡和坏死性凋亡之间相互高度关联,相互补偿以促进细胞死亡,促进疾病发生发展[47]。在脓毒症 ALI 的研究中,小鼠模型不仅表现出脂质过氧化损伤、铁含量和肺前列腺素内过氧化物合成酶 2(prostaglandin-endoperoxide synthase 2,PTGS2)蛋白表达增加、GPX4 蛋白表达降低,还表现出 NLRP3 炎症小体的增多和焦亡相关蛋白的表达,由此可见在此过程中铁死亡和焦亡相互串扰,而上述过程可被线粒体醛脱氢酶 2 所逆转[48]。

细胞死亡之间的相互串扰机制将在未来的研究中不断明了,而阐明何时以及如何使用治疗策略调节其串扰的中心环节,同时阻断多种死亡方式的启动,将成为未来研究中的重中之重。

表 1 脓毒症急性肺损伤的治疗靶点-抑制铁死亡

Table 1 Therapeutic target of sepsis-associated acute lung injury-inhibt ferroptosis

干预化合物/方式 Interventional compounds/methods	损伤细胞类型 Damaged cell types	机制 Mechanism	指标监测及变化 Indicators monitoring and changes
微小 RNA-125b-5p[20] miR-125b-5p	肺微血管内皮细胞 Pulmonary microvascular endothelial cells	Kelch 样 ECH 相关蛋白 1/核因子 E2 相关因子 2/血红素加氧酶-1 Keap1/Nrf2/HO-1	死亡率↓;肺组织干湿比重↓;肺组织病理损伤评分↓;谷胱甘肽过氧化物酶 4↑;谷胱甘肽↑;活性氧↓;丙二醛↓;4-羟基壬烯酸↓;超氧化物歧化酶↑;过氧化氢酶↑;核因子 E2 相关因子 2↑;血红素加氧酶-1↑;Kelch 样 ECH 相关蛋白 1↓;铁离子还原抗氧化能力↑;线粒体膜电位↑ Mortality↓;Lung wet/dry weight ratio↓;Lung injury score↓;GPX4↑;GSH↑;ROS↓;MDA↓;4-HNE↓;SOD↑;CAT↑;Nrf2↑;HO-1↑;Keap1↓;FRAP↑;MMP↑
敲除环状 RNA EXOC5[22] Knock down circEXOC5	微血管内皮细胞 Microvascular endothelial cells	多聚嘧啶区结合蛋白 1/酶酰基辅酶 A 合成酶长链 4 PTBP1/ACSL4	死亡率↓;肺组织病理损伤↓;细胞活力↑;谷胱甘肽过氧化物酶 4↑;活性氧↓;Fe^{2+}↓;丙二醛↓;4-羟基壬烯酸↓;酶酰基辅酶 A 合成酶长链 4↓;多聚嘧啶区结合蛋白 1↓ Mortality↓;Lung injury↓;Cell viability↑;GPX4↑;ROS↓;Fe^{2+}↓;MDA↓;4-HNE↓;ACSL4↓;PTBP1↓
抑制前列腺六段跨膜上皮抗原 1[23] Inhibit six-segment transmembrane epithelial antigen of prostate 1	肺微血管内皮细胞 Pulmonary microvascular endothelial cells	溶质转运家族 7A11/谷胱甘肽过氧化物酶 4 SLC7A11/GPX4	细胞活力↑;线粒体损伤↓;白介素-1β↓;白介素-6↓;细胞间黏附分子 1↓;谷胱甘肽过氧化物酶 4↑;谷胱甘肽↑;Fe^{2+}↓;活性氧↓;丙二醛↓;核因子 E2 相关因子 2↑;溶质转运家族 7A11↑ Cell viability↑;Mitochondria injury↓;IL-1β↓;IL-6↓;ICAM-1↓;GPX4↑;GSH↑;Fe^{2+}↓;ROS↓;MDA↓;Nrf2↑;SLC7A11↑
谷胱甘肽过氧化物酶 4[24] Glutathione peroxidase 4	肺上皮细胞 Lung epithelial cells	GPX4 的 m^6A 修饰 GPX4 m^6A modification	细胞活力↑;活性氧↓;Fe^{2+}↓;肺组织病理损伤;谷胱甘肽过氧化物酶 4;谷胱甘肽;丙二醛 Cell viability↑;ROS↓;Fe^{2+}↓;Lung injury;GPX4;GSH;MDA
Yes 相关蛋白 1[25] Yes-associated protein 1	肺上皮细胞 Lung epithelial cells	铁蛋白自噬 Ferritinophagy	肺组织病理损伤↓;细胞活力↑;线粒体损伤↓;谷胱甘肽过氧化物酶 4↑;谷胱甘肽↑;Fe^{2+}↓;铁蛋白重链 1↑;丙二醛↓;活性氧↓;酶酰基辅酶 A 合成酶长链 4↓;溶质转运家族 7A11↑;线粒体铁离子转运蛋白↓;核受体共激活因子 4↓ Lung injury↓;Cell viability↑;Mitochondria injury↓;GPX4↑;GSH↑;Fe^{2+}↓;FTH1↑;MDA↓;ROS↓;ACSL4↓;SLC7A11↑;SFXN1↓;NCOA4↓
阿魏酸[3] Ferulic acid	肺泡上皮细胞 Alveolar epithelial cells	核因子 E2 相关因子 2/血红素加氧酶-1 Nrf2/HO-1	肺组织病理损伤↓;肺组织干湿比重↓;肺泡灌洗液总蛋白↓;细胞活力↑;谷胱甘肽过氧化物酶 4↑;谷胱甘肽↑;丙二醛↓;Fe^{2+}↓;活性氧↓;髓过氧化物酶↓;核因子 E2 相关因子 2↑;血红素加氧酶-1↑;闭锁小带蛋白 1↑;闭锁蛋白 1↑;紧密连接蛋白 1↑;细胞通透性↓ Lung injury↓;Lung wet/dry weight ratio↓;Total bronchoalveolar lavage fluid protein↓;Cell viability↑;GPX4↑;GSH↑;MDA↓;Fe^{2+}↓;ROS↓;MPO↓;Nrf2↑;HO-1↑;ZO-1↑;Occludin↑;Claudin-1↑;Cell permeability↓

续表1

干预化合物/方式 Interventional compounds/methods	损伤细胞类型 Damaged cell types	机制 Mechanism	指标监测及变化 Indicators monitoring and changes
富含 AU 元件的 RNA 结合因子 1[28] AU-rich element-RNA binding factor 1	肺泡上皮细胞 Alveolar epithelial cells	调节核因子 E2 相关因子 2 和激活转录因子 3 Regulate NRF2 and ATF3	肺组织病理损伤↓;肺组织干湿比重↓;细胞活力↑;谷胱甘肽过氧化物酶 4↑;谷胱甘肽↑;总铁↓;丙二醛↓;髓过氧化物酶↓;细胞中脂质过氧化物↓;肿瘤坏死因子-α↓;白介素-1β↓;白介素-6↓;核因子 E2 相关因子 2↑;血红素加氧酶-1↑;酶酰基辅酶 A 合成酶长链 4↓;溶质转运家族 7A11↑;激活转录因子 3↓ Lung injury↓; Lung wet/dry weight ratio↓; Cell viability↑; GPX4↑; GSH↑; Iron↓; MDA↓; MPO↓;细胞中脂质过氧化物↓;TNF-α↓;IL-1β↓;IL-6↓;Nrf2↑;HO-1↑;ACSL4↓;SLC7A11↑;ATF3↓
组织再生相关性保护素 1[30] Protectin conjugates in tissue regeneration 1	肺上皮细胞 Lung epithelial cells	脂氧素 A4/蛋白激酶 A/cAMP 反应元件结合蛋白 ALX/PKA/CREB	肺组织病理损伤↓;细胞活力↑;线粒体损伤↓;肿瘤坏死因子-α↓;白介素-1β↓;白介素-6↓;谷胱甘肽过氧化物酶 4↑;谷胱甘肽↑;活性氧↓;丙二醛↓;4-羟基壬烯酸↓;前列腺素内过氧化物合酶↓;Fe^{2+}↓;磷酸化蛋白激酶 A/蛋白激酶 A↑;磷酸化 cAMP 反应元件结合蛋白/cAMP 反应元件结合蛋白↑ Lung injury↓;Cell viability↑;Mitochondria injury↓; TNF-α↓; IL-1β↓; IL-6↓; GPX4↑; GSH↑; ROS↓; MDA↓; 4-HNE↓; PTGS2↓; Fe^{2+}↓; p-PKA/PKA↑; p-CREB/CREB↑
衣康酸[32] Itaconate	巨噬细胞 Macrophages	核因子 E2 相关因子 2 Nrf2	肺组织病理损伤↓;肺组织干湿比重↓;细胞活力↑;肿瘤坏死因子-α↓;白介素-1β↓;白介素-6↓;谷胱甘肽过氧化物酶 4↑;谷胱甘肽↑;活性氧↓;总铁↓;丙二醛↓;4-羟基壬烯酸↓;核因子 E2 相关因子 2↑;血红素加氧酶-1↑;溶质转运家族 7A11↑;前列腺素内过氧化物合酶 2↓;谷氨酸-半胱氨酸连接酶修饰亚基↑ Lung injury↓; Lung wet/dry weight ratio↓; Cell viability↑; TNF-α↓; IL-1β↓; IL-6↓; GPX4↑; GSH↑; ROS↓; Iron↓; MDA↓; 4-HNE↓; Nrf2↑; HO-1↑; SLC7A11↑; PTGS2↓; GCLM↑
尿苷[37] Uridine	巨噬细胞 Macrophages	核因子 E2 相关因子 2 Nrf2	肺组织病理损伤↓;肺组织干湿比重↓;细胞活力↑;肺泡灌洗液总蛋白↓;谷胱甘肽过氧化物酶 4↑;谷胱甘肽↑;活性氧↓;总铁↓;丙二醛↓;髓过氧化物酶↓;还原脂质/氧化脂质↑;肿瘤坏死因子-α↓;白介素-1β↓;白介素-6↓;核因子 E2 相关因子 2↑;血红素加氧酶 1↑;溶质转运家族 7A11↑;酶酰基辅酶 A 合成酶长链 4↓ Lung injury↓; Lung wet/dry weight ratio↓; Cell viability↑; Total bronchoalveolar lavage fluid protein↓;GPX4↑; GSH↑; ROS↓; Iron↓; MDA↓; MPO↓; R-bodipy/O-bodipy↑; TNF-α↓; IL-1β↓; IL-6↓;Nrf2↑;HO1↑;SLC7A11↑;ACSL4↓
硫化氢[39] H_2S	巨噬细胞 Macrophages	哺乳动物雷帕霉素靶蛋白 mTOR	死亡率↓;肺组织干湿比重↓;肺组织病理损伤↓;白介素-1β↓;白介素-18↓;白介素-17↓;丙二醛↓;超氧化物歧化酶↑;谷胱甘肽还原酶活性系数↑;铁蛋白↑;铁蛋白轻链↑;环氧化酶 2↓;NADPH 氧化酶 1↓;溶质转运家族 7A11↑;苄氯素 1↓;微管相关蛋白 1 的轻链 3- II/I↑ Mortality↓;Lung wet/dry weight ratio↓;Lung injury↓;IL-1β↓; IL-18↓; IL-17↓; MDA↓; SOD↑; GRAC↑;Ferritin↑;Ferritin light chain↑;COX2↓; NOX1↓;SLC7A11↑;Beclin1↓;LC3-II/LC3-I↑

4 展望

越来越多的证据表明,铁死亡不仅在脓毒症 ALI 疾病过程中发挥重要作用,在脓毒症多器官损伤中也占据重要地位,抑制铁死亡可显著缓解相应器官损伤,包括心脏损伤[49]、肝损伤[50]、急性肾损伤[51]、脑损伤[52]等。因此,抑制铁死亡或可作为脓毒症的一种新型潜在治疗策略。然而,铁死亡调控治疗的临床意义和治疗潜力也仍需进一步评估。因此,在未来的工作中,深入阐明铁死亡或细胞死亡之间的串扰在脓毒症 ALI 中发挥的具体作用、探索其全过程通路与疾病预后的关系等,将有望为脓毒症 ALI 的治疗提供新的潜在靶点和治疗策略。

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