基于线粒体功能的阿霉素诱导心脏毒性的分子机制及中药研究进展

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摘要 蒽环类化疗药阿霉素(doxorubicin, DOX)是治疗各种癌症最有效的药物之一, 然而其治疗效应受到相关心脏毒性的严重限制. 尽管该领域研究众多, 但DOX诱导心脏毒性(DOX-induced cardiotoxicity, DIC)的确切分子机制仍然值得进一步研究. DOX是一种线粒体毒素, 线粒体损伤是DIC的核心. 本文回顾大量文献并收集与DIC相关的依赖于线粒体功能障碍的机制, 包括DOX对线粒体电子传递链、氧化还原循环、氧化应激、钙失调、细胞凋亡途径和线粒体自噬等的影响. 此外, 本文讨论了基于线粒体功能的中药预防和/或减轻DIC的现有策略, 以期作为DOX与中药的临床联合用药提供科学依据.

关键词 阿霉素, 心脏毒性, 线粒体功能, 中药

以阿霉素(doxorubicin, DOX)为代表的蒽环类药物是一类能够治疗不同类型恶性肿瘤的高效化疗药. 尽管应用广泛, 但DOX诱导心脏毒性(DOX-induced cardiotoxicity, DIC)极大限制了其临床治疗效果^[1,2]. 根据DIC的阶段进展和临床表现, 使用肌钙蛋白等生物标记物的心肌损伤可在治疗期间或治疗后不久被识别, DOX治疗后数月内发生的左心室射血分数(left ventricular ejection fraction, LVEF)降低可被定义为早期, DOX治疗数年后诊断的心力衰竭(heart failure, HF)症状可以定义为晚期^[3,4]. 据统计, DOX累积治疗剂量 $>350 \text{ mg/m}^2$ 时, LVEF呈剂量依赖性降低; 累积剂量达

550 mg/m^2 时, HF患病率急剧增加; 随着患者DOX累积治疗剂量的增加, DOX相关充血性HF患者的百分比逐渐增加, 且在累积剂量方案完成后呈现不可逆性^[5~7].

DOX通过多种机制发挥作用, 由于DOX触发的信号通路存在交互错杂的联系, 目前尚不清楚其最核心的机制. 许多研究支持DOX诱导活性氧(reactive oxygen species, ROS)的产生及其导致的脂质过氧化、钙失调和能量代谢紊乱最终导致HF的观点^[8~11]. 但其毒性的潜在分子机制仍未完全阐明. DOX是一种线粒体毒素, 线粒体损伤是DOX诱导心脏功能障碍和细胞死亡的核心^[12,13]. 心肌细胞需要大量功能正常的线粒体,

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以确保产生足够的ATP实现舒缩功能和细胞存活。因此, 本文系统总结了DIC发病过程中线粒体功能相关的信号转导病生理机制。此外, 还回顾了各种中药预防和治疗DIC的策略, 以期全面梳理其潜在治疗靶点和干预药物。

1 DIC的分子机制

1.1 ROS的产生

线粒体是细胞暴露于DOX时受损最严重的细胞器。DIC的主要机制之一与线粒体功能障碍密切相关, 能显著诱导细胞内ROS和氧化应激^[14]。心磷脂是存在于线粒体内膜的一种磷脂, 对维持线粒体结构、功能、能量代谢和细胞存活至关重要, 而DOX与心磷脂之间存在高亲和力, 致使DOX易在线粒体内膜中积累, 并通过氧化应激介导线粒体毒性^[15]。此外, 心磷脂和DOX之间的静电结合导致电子传递链(electron transfer chain, ETC)中复合物I, III和IV的活性降低或丧失^[16]。并且研究还表明, 复合物I可催化DOX还原为半醌自由基, 进而氧化形成超氧阴离子并导致ETC的进一步破坏^[17]。另外, DOX也易被内皮型一氧化氮合酶还原为半醌, 再通过氧化还原循环产生超氧自由基加剧线粒体毒性^[18,19]。

线粒体中DOX积累也引起ROS的增加^[19,20]。这些活性物质反过来引起脂质过氧化、DNA和蛋白质的氧化损伤, 导致线粒体DNA(mitochondrial DNA, mtDNA)受损、ATP水平下降、心磷脂过氧化和线粒体通透性转变^[2]。最终, ROS、mtDNA损伤和ETC之间的密切相互作用导致恶性循环的形成, 进而细胞色素c及凋亡因子释放, 启动细胞凋亡途径。由此可见, 即使临床抗氧化剂的使用效果并不令人满意, 抑制ROS和氧化应激仍然是抗DIC不容忽视的关键点。

1.2 凋亡途径

DOX可通过内在和外在两种途径激活细胞凋亡^[21,22]。其中, 线粒体依赖性内在途径在DIC中起关键作用, 在该通路中促凋亡蛋白如Bax上调激活, 促进线粒体细胞色素c的释放, 导致caspase-9和caspase-3的级联激活。研究表明, 细胞外调节蛋白激酶(extracellular regulated protein kinase, ERK)/p53通路和活化的核因子- κ B(nuclear factor, NF- κ B)依赖的p53通路是DOX诱

导心肌细胞凋亡的关键调控介质^[23]。也有研究表明, DIC是由Bnip3的上调介导的, Bnip3通过促进线粒体通透性转换孔(mitochondrial permeability transition pore, mPTP)形成导致线粒体去极化, 从而导致细胞凋亡^[24]。

此外, DOX也可通过外在途径介质如死亡受体(death receptors, DRs)介导心肌细胞凋亡。研究表明, DOX可诱导肿瘤坏死因子相关凋亡诱导配体(TNF-related apoptosis-inducing ligand, TRAIL), Fas, DR4和DR5等DR的上调, 触发caspase级联反应, 最终导致细胞凋亡^[25]。此外, 也有研究鉴定出一条涉及线粒体凋亡诱导因子(apoptosis-inducing factor, AIF)作用的半胱天冬酶非依赖性途径, AIF引起大规模DNA损伤、p53表达增强等, 这也提示单纯的caspase抑制剂并不能完全阻止DIC诱导的凋亡^[26,27]。临床前和临床证据均表明, 心肌细胞凋亡是DOX治疗肿瘤的急性和慢性副作用。总之, 抑制心肌细胞凋亡是DIC发展不同阶段的共同治疗策略。

1.3 钙失调

钙失调是DIC另一种被广泛认识的机制, DOX引起细胞内 Ca^{2+} 增加, 产生ROS进而诱导细胞凋亡^[28]。已知DOX的羟基代谢物通过多种机制抑制钠钙交换通道, 影响钙稳态, 包括调节肌浆网的肌/内质网 Ca^{2+} ATP酶和肌膜上的钠/钾泵^[29]。并且与DOX相比, 消除代谢物更困难。另外, 有研究表明, 负责钙转运的肌浆网蛋白的基因水平降低是DIC中钙稳态改变的根本原因^[30]。此外, 其他研究还发现了钙调神经磷酸酶(一种钙依赖性磷酸酶)在DOX触发Fas介导细胞凋亡中的关键作用^[31]。有趣的是, 研究发现DOX诱导mtDNA耗竭及其相关的ETC损伤先于钙失调, 这对DIC的分阶段靶向治疗具有重要提示意义。

钙通道的失调导致钙负荷增加, 从而导致线粒体的钙储存能力下降^[28]。这导致环孢素敏感钙通道的激活, 进一步加剧了钙负荷。因此, 细胞质中钙浓度的增加会导致线粒体功能障碍和细胞凋亡^[32]。因此, 靶向钙功能障碍是治疗DIC的另一种可行方案。

1.4 线粒体自噬

靶向有缺陷的线粒体实现自噬消除即线粒体自噬, 这一过程有助于维持线粒体质量控制系统。

PINK1/Parkin介导的线粒体自噬发生在受损/去极化的线粒体中^[33]. 研究报道, DIC模型5天时Parkin介导的线粒体自噬水平降低, 2周后线粒体自噬水平反弹且联合自噬抑制剂具有保护效应, 提示过度线粒体自噬对心脏不利^[34]. 而随着时间延长, DOX诱导p53增加, 与Parkin相互作用并将其隔离到细胞质中, 导致Parkin向线粒体的易位减少和线粒体自噬能力降低, 最终受损线粒体累积导致心脏毒性^[35,36]. 另外, DOX的这种效应在p53缺陷小鼠中未观察到, 并且可以通过在新生乳鼠心肌细胞中过度表达Parkin来抵消. 由此可见, 线粒体自噬在DIC不同发展阶段的变化具有动态性, 基于调控线粒体自噬的治疗策略具有一定挑战性.

FUNDC1是一种线粒体外膜蛋白, 具有LIR基序, 因此能与LC3-II相互作用, 并与线粒体自噬有关^[37,38]. 尽管研究了缺氧诱导的线粒体自噬, DOX在FUNDC1介导的线粒体自噬中的作用仍有待确定.

1.5 线粒体拓扑异构酶-II β

DOX的另一个靶点是拓扑异构酶-II, 作用效应是诱导DNA单链/双链断裂. DOX通过插入癌细胞的DNA并形成共价加合物从而抑制DNA聚合酶和核酸合成, 杀死快速增殖的癌细胞^[39]. 此外, DOX将拓扑异构酶-II α (TOPII α)与DNA交联, 形成TOPII α -DOX-DNA复合物, 导致DNA断裂和细胞死亡, 这是杀死表达高水平TOPII α 癌细胞的主要机制. 与肿瘤细胞不同, 心肌细胞不表达TOPII α , 大量表达TOPII β 于心肌细胞线粒体中, 因此可形成DNA-TOPII β -DOX复合物, 导致双链断裂和细胞死亡. 并且一项心肌细胞特异性TOPII β 敲除实验证实了TOPII β 是DIC病理机制的关键因素^[40-42]. 还有研究表明, 由TOPII β 介导的DOX诱导DNA损伤显著改变线粒体转录组, 降低了线粒体生物发生^[43].

目前, 唯一被美国食品和药物监督管理局(U.S. Food and Drug Administration, FDA)批准的预防DIC的药物——右雷佐生, 其针对TOPII β 的机理进一步证实了该机制的特异性作用^[44]. 另外, 也有研究报道右雷佐生通过促进TOPII β 降解而非铁螯合来防止双链断裂^[45]. 尽管药理机制明确, 右雷佐生未能达到临床前研究的预期, 同时也引发了对其安全性的担忧. 因此, 进一步研究开发靶向TOPII β 同时低毒副作用的药物至关重要.

2 DIC整体动物模型和离体细胞模型的应用

现有文献中广泛报道了多种DIC整体动物模型和离体细胞模型. 其中, 动物模型包括: (i) 以冠状动脉微导管注射阿霉素(每次0.45 mg/kg)法构建DIC小型猪模型, 每两周注射一次. 通过多参数心脏磁共振检查评估, 结果证实, 第三次注射后2周, 在T1加权像和细胞外容积均正常的情况下, T2弛豫时间延长所识别的心肌水肿为早期DIC心肌损伤标志, 且该阶段为DIC可逆阶段^[46]. 因此, 以每两周注射一次阿霉素, 连续三次造模的方法构建小型猪DIC早期疾病模型以探讨中药与阿霉素联合使用防治DIC具有巨大应用前景. (ii) 以尾静脉注射阿霉素(每次5 mg/kg)法构建DIC小鼠模型, 通过每周注射一次, 连续4周造模以模拟临床阿霉素毒性累积过程^[47], 该模型对寻找提高DIC晚期心功能的中药治疗策略具有重要指导意义. 本课题组^[48,49]前期基于小鼠DIC晚期模型筛选出丹参酮类化合物和弥罗松酚, 其具有显著保护作用. 此外, 尾静脉一次性注射高剂量阿霉素(每次20 mg/kg)小鼠模型也是适用于研究DIC早期的疾病模型, 本课题组^[50]基于此模型, 证实DIC早期给予自噬激动剂反而加重心功能损伤. 相比于尾静脉注射法, 小鼠腹腔注射阿霉素消化道反应较大, 在近年来的研究中应用逐渐减少. 针对细胞模型, 研究指出大于2 $\mu\text{mol/L}$ 的阿霉素浓度不具有临床相关性^[51], 因此大多数研究采用1 $\mu\text{mol/L}$ 阿霉素诱导心肌细胞或内皮细胞模型. 有研究显示, 阿霉素诱导18 h以内没有检测到心肌细胞ATP水平的变化^[43], 因此通常以阿霉素诱导心肌细胞不少于18 h进行ATP依赖的相关机制研究. 另有研究显示, 阿霉素诱导24 h引起内皮细胞的细胞周期停滞^[52], 因此阿霉素损伤内皮细胞的研究通常以24 h诱导为主.

3 中药抗DIC的研究进展

目前, 右雷佐生、他汀类药物、血管紧张素转换酶抑制剂、钙通道阻滞剂、 β -受体阻滞剂等几类心脏保护剂已在动物和临床试验中得到开发和测试, 但仍未取得满意疗效或存在较大毒副作用风险^[53,54]. 比如, 研究证实非选择性 β -受体阻滞剂卡维地洛与DOX联合治疗DIC大鼠模型能改善心肌线粒体功能, 提高钙负

荷能力^[55], 但临床研究提示卡维地洛能引起心跳过缓、体位性低血压、心衰加重等症状。此外, 阿替洛尔虽然也属于非选择性 β -受体阻滞剂, 却没有抗DIC效果^[56], 因此 β -受体阻滞剂抗DIC的确切药效及机制有待进一步确认。再如, 右雷佐生通过作用于心脏拓扑异构酶抑制DOX诱导的DNA断裂, 但因其诱导骨髓移植和继发恶性肿瘤的毒副作用被欧洲药监局限制使用^[57]。因此, 安全性较好的中医药为DIC的干预治疗提供了广阔的空间。

丹参是中医药治疗心血管疾病使用频次最高的药物之一, 丹参酮是丹参的活性脂溶成分, 临床疗效确切。基于此, 本课题组前期开展了深入药理研究, 证实二氢丹参酮 I (dihydrotanshinone I)、丹参酮 II A (tanshinone II A) 和隐丹参酮 (cryptotanshinone) 保护DIC的机制均与抑制心肌细胞凋亡相关, 有趣的是, 相比单独使用DOX, 丹参酮 II A 与DOX联合应用增效减毒^[49,58,59]。此外, 其他中草药活性成分也对DIC诱导的线粒体功能障碍显示出良好的保护作用。例如, 木犀草素 (luteolin) 通过调控dynamitin-related protein 1(Drp1)/mammalian target of rapamycin(mTOR)/transcription

factor EB(TFEB)依赖机制促进线粒体自噬, 恢复线粒体功能和减少细胞凋亡以保护DIC, 木犀草素联合DOX也可提高其抗肿瘤活性^[60,61]。大黄酚(chrysophanol)通过抑制凋亡和恢复线粒体稳态来保护心肌细胞免受DOX损伤^[62]。海胆色素A(echinochrome A)通过提高线粒体膜电位, 降低ROS水平, 保持线粒体氧化磷酸化和三磷酸腺苷水平以保护DIC^[63]。紫檀芪(pterostilben)通过激活peroxisome proliferator-activated receptor gamma coactivator-1 alpha(PGC-1 α)来保护DIC, 增强adenosine monophosphate-activated protein kinase (AMPK)和Sirtuin 1(SIRT1)级联反应减少氧化应激^[64]。芝麻素(sesamin)对DIC的保护机制与减轻氧化应激损伤有关, 部分通过激活SIRT1^[65]。以抗氧化和抗癌闻名的姜黄素(curcumin)对癌细胞和心肌细胞具有协同作用, 可降低心肌细胞凋亡而促进癌细胞凋亡^[66]。黄酮类化合物(flavonoids)具有很强的抗氧化活性, 其中白藜芦醇(resveratrol)通过激活AMPK减轻DIC中的氧化应激和细胞凋亡^[67]。另外, 大量研究也证实, 其他黄酮类, 如毛茛异黄酮(calycosin)、蛇床子(osthole)、染料木素(genistein)、香豆素(coumestrol)等可通过抗氧化

图1 DIC线粒体相关治疗靶点以及针对每个靶点的潜在中药

Figure 1 DIC mitochondrial related therapeutic targets and potential traditional Chinese medicine for each target

和减少凋亡保护DIC.

4 展望

本文系统梳理了基于线粒体功能DIC已知的病理机制: DIC与心脏组织中增加的氧化应激直接相关; 氧化应激的增加导致ROS的产生; DIC还涉及导致细胞凋亡的 Ca^{2+} 水平的改变; 随着半胱天冬酶的激活, 心肌细胞发生凋亡; 线粒体自噬的失调未能及时清除受损

线粒体也会加剧DIC(图1). 此外, 本文总结了一些潜在的中药相关研究(图1). 虽然现有报道显示中药复方及活性成分对DIC保护作用显示出巨大的应用开发前景, 但大多数证据均来自临床前研究, 因此在临床实践中进行深入的验证非常必要. 另外, 在进行临床试验之前, 必须确保中药相关产品具有足够的生物利用度, 尤其是那些已知水溶性低且会引起广泛代谢的中草药. 因此, 设计定制的药物递送系统, 以优化生物利用度是未来进一步围绕DIC开发有效药物的重要方向.

参考文献

- 1 Vejpongs P, Yeh E T H. Prevention of anthracycline-induced cardiotoxicity. *J Am Coll Cardiol*, 2014, 64: 938–945
- 2 Rawat P S, Jaiswal A, Khurana A, et al. Doxorubicin-induced cardiotoxicity: an update on the molecular mechanism and novel therapeutic strategies for effective management. *Biomed pharmacother*, 2021, 139: 111708
- 3 Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*, 2015, 131: 1981–1988
- 4 Li J, Chang H M, Banchs J, et al. Detection of subclinical cardiotoxicity in sarcoma patients receiving continuous doxorubicin infusion or pre-treatment with dexrazoxane before bolus doxorubicin. *Cardiooncology*, 2020, 6: 1
- 5 Ky B, Putt M, Sawaya H, et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol*, 2014, 63: 809–816
- 6 Renu K, V.g. A, P.b. T P, et al. Molecular mechanism of doxorubicin-induced cardiomyopathy—an update. *Eur J Pharmacol*, 2018, 818: 241–253
- 7 Nebigil C G, Désaubry L. Updates in anthracycline-mediated cardiotoxicity. *Front Pharmacol*, 2018, 9: 1262
- 8 Koleini N, Nickel B E, Edel A L, et al. Oxidized phospholipids in doxorubicin-induced cardiotoxicity. *Chem Biol Interact*, 2019, 303: 35–39
- 9 Govender J, Loos B, Marais E, et al. Mitochondrial catastrophe during doxorubicin-induced cardiotoxicity: a review of the protective role of melatonin. *J Pineal Res*, 2014, 57: 367–380
- 10 Clayton Z S, Brunt V E, Hutton D A, et al. Doxorubicin-induced oxidative stress and endothelial dysfunction in conduit arteries is prevented by mitochondrial-specific antioxidant treatment. *JACC Cardiooncol*, 2020, 2: 475–488
- 11 Adhikari A, Asdaq S M B, Al Hawaj M A, et al. Anticancer drug-induced cardiotoxicity: insights and pharmacogenetics. *Pharmaceuticals*, 2021, 14: 970
- 12 Wallace K B, Sardão V A, Oliveira P J. Mitochondrial determinants of doxorubicin-induced cardiomyopathy. *Circ Res*, 2020, 126: 926–941
- 13 O'Brien C G, Ozen M O, Ikeda G, et al. Mitochondria-rich extracellular vesicles rescue patient-specific cardiomyocytes from doxorubicin injury. *JACC Cardiooncol*, 2021, 3: 428–440
- 14 Songbo M, Lang H, Xinyong C, et al. Oxidative stress injury in doxorubicin-induced cardiotoxicity. *Toxicol Lett*, 2019, 307: 41–48
- 15 Goormaghtigh E, Chatelain P, Caspers J, et al. Evidence of a specific complex between adriamycin and negatively-charged phospholipids. *Biochim Biophys Acta*, 1980, 597: 1–14
- 16 Prathumsap N, Shinlapawittayatorn K, Chattipakorn S C, et al. Effects of doxorubicin on the heart: from molecular mechanisms to intervention strategies. *Eur J Pharmacol*, 2020, 866: 172818
- 17 Fu J, Yamamoto K, Guan Z W, et al. Human neuronal nitric oxide synthase can catalyze one-electron reduction of adriamycin: role of flavin domain. *Arch Biochem Biophys*, 2004, 427: 180–187
- 18 Octavia Y, Tocchetti C G, Gabrielson K L, et al. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. *J Mol Cell Cardiol*, 2012, 52: 1213–1225
- 19 Vásquez-Vivar J, Martasek P, Hogg N, et al. Endothelial nitric oxide synthase-dependent superoxide generation from adriamycin. *Biochemistry*, 1997, 36: 11293–11297

- 20 Šimůnek T, Štěrba M, Popelová O, et al. Anthracycline-induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron. *Pharmacol Rep*, 2009, 61: 154–171
- 21 Zhang X, Hu C, Kong C Y, et al. FNDC5 alleviates oxidative stress and cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity via activating AKT. *Cell Death Differ*, 2020, 27: 540–555
- 22 Kankeu C, Clarke K, Passante E, et al. Doxorubicin-induced chronic dilated cardiomyopathy—the apoptosis hypothesis revisited. *J Mol Med*, 2017, 95: 239–248
- 23 Zhang D X, Ma D Y, Yao Z Q, et al. ERK1/2/p53 and NF-κB dependent-PUMA activation involves in doxorubicin-induced cardiomyocyte apoptosis. *Eur Rev Med Pharmacol Sci*, 2016, 20: 2435–2442
- 24 Zheng X, Zhong T, Ma Y, et al. Bnip3 mediates doxorubicin-induced cardiomyocyte pyroptosis via caspase-3/GSDME. *Life Sci*, 2020, 242: 117186
- 25 Zhao L, Zhang B. Doxorubicin induces cardiotoxicity through upregulation of death receptors mediated apoptosis in cardiomyocytes. *Sci Rep*, 2017, 7: 44735
- 26 Moreira A C, Branco A F, Sampaio S F, et al. Mitochondrial apoptosis-inducing factor is involved in doxorubicin-induced toxicity on H9c2 cardiomyoblasts. *Biochim Biophys Acta*, 2014, 1842: 2468–2478
- 27 Yang L, Liu X, Lu Z, et al. Ursolic acid induces doxorubicin-resistant HepG2 cell death via the release of apoptosis-inducing factor. *Cancer Lett*, 2010, 298: 128–138
- 28 Park K H, Kim S Y, Gul R, et al. Fatty acids ameliorate doxorubicin-induced intracellular Ca^{2+} increase and apoptosis in rat cardiomyocytes. *Biol Pharm Bull*, 2008, 31: 809–815
- 29 Zuo S, Kong D, Wang C, et al. CTRH2 promotes endoplasmic reticulum stress-induced cardiomyocyte apoptosis through m-calpain. *EMBO Mol Med*, 2018, 10: e8237
- 30 Keung E C, Toll L, Ellis M, et al. L-type cardiac calcium channels in doxorubicin cardiomyopathy in rats morphological, biochemical, and functional correlations. *J Clin Invest*, 1991, 87: 2108–2113
- 31 Lim C C, Zuppinger C, Guo X, et al. Anthracyclines induce calpain-dependent titin proteolysis and necrosis in cardiomyocytes. *J Biol Chem*, 2004, 279: 8290–8299
- 32 Guo R, Hua Y, Ren J, et al. Cardiomyocyte-specific disruption of Cathepsin K protects against doxorubicin-induced cardiotoxicity. *Cell Death Dis*, 2018, 9: 692
- 33 Onishi M, Yamano K, Sato M, et al. Molecular mechanisms and physiological functions of mitophagy. *EMBO J*, 2021, 40: e104705
- 34 Hoshino A, Mita Y, Okawa Y, et al. Cytosolic p53 inhibits Parkin-mediated mitophagy and promotes mitochondrial dysfunction in the mouse heart. *Nat Commun*, 2013, 4: 2308
- 35 Catanzaro M P, Weiner A, Kaminaris A, et al. Doxorubicin-induced cardiomyocyte death is mediated by unchecked mitochondrial fission and mitophagy. *FASEB J*, 2019, 33: 11096–11108
- 36 Liang X, Wang S, Wang L, et al. Mitophagy inhibitor liensinine suppresses doxorubicin-induced cardiotoxicity through inhibition of Drp1-mediated maladaptive mitochondrial fission. *Pharmacol Res*, 2020, 157: 104846
- 37 Lampert M A, Orogo A M, Najor R H, et al. BNIP3L/NIX and FUNDC1-mediated mitophagy is required for mitochondrial network remodeling during cardiac progenitor cell differentiation. *Autophagy*, 2019, 15: 1182–1198
- 38 Zhang W, Siraj S, Zhang R, et al. Mitophagy receptor FUNDC1 regulates mitochondrial homeostasis and protects the heart from I/R injury. *Autophagy*, 2017, 13: 1080–1081
- 39 Press M F, Sauter G, Buyse M, et al. Alteration of topoisomerase II-α gene in human breast cancer: association with responsiveness to anthracycline-based chemotherapy. *J Clin Oncol*, 2011, 29: 859–867
- 40 Lyu Y L, Kerrigan J E, Lin C P, et al. Topoisomerase IIβ-mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. *Cancer Res*, 2007, 67: 8839–8846
- 41 Tokarska-Schlattner M, Lucchinetti E, Zaugg M, et al. Early effects of doxorubicin in perfused heart: transcriptional profiling reveals inhibition of cellular stress response genes. *Am J Physiol Regul Integr Comp Physiol*, 2010, 298: R1075–R1088
- 42 Hasinoff B B, Patel D, Wu X. The role of topoisomerase IIβ in the mechanisms of action of the doxorubicin cardioprotective agent dexrazoxane. *Cardiovasc Toxicol*, 2020, 20: 312–320
- 43 Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med*, 2012, 18: 1639–1642

- 44 van Dalen E C, Caron H N, Dickinson H O, et al. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev*, 2011, 6: CD003917
- 45 Deng S, Yan T, Jendry C, et al. Dexrazoxane may prevent doxorubicin-induced DNA damage via depleting both topoisomerase II isoforms. *BMC Cancer*, 2014, 14: 842
- 46 Galán-Arriola C, Lobo M, Vilchez-Tschischke J P, et al. Serial magnetic resonance imaging to identify early stages of anthracycline-induced cardiotoxicity. *J Am Coll Cardiol*, 2019, 73: 779–791
- 47 Li D L, Wang Z V, Ding G, et al. Doxorubicin blocks cardiomyocyte autophagic flux by inhibiting lysosome acidification. *Circulation*, 2016, 133: 1668–1687
- 48 Li W, Cao J, Wang X, et al. Ferruginol restores SIRT1-PGC-1 α -mediated mitochondrial biogenesis and fatty acid oxidation for the treatment of DOX-induced cardiotoxicity. *Front Pharmacol*, 2021, 12: 773834
- 49 Wang X, Li C, Wang Q, et al. Tanshinone IIA restores dynamic balance of autophagosome/autolysosome in doxorubicin-induced cardiotoxicity via targeting Beclin1/LAMP1. *Cancers*, 2019, 11: 910
- 50 Wang Y, Lu X, Wang X, et al. *atg7*-based autophagy activation reverses doxorubicin-induced cardiotoxicity. *Circ Res*, 2021, 129: e166–e182
- 51 Minotti G, Menna P, Salvatorelli E, et al. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev*, 2004, 56: 185–229
- 52 Paoli E E, Ingham E S, Zhang H, et al. Accumulation, internalization and therapeutic efficacy of neuropilin-1-targeted liposomes. *J Control Release*, 2014, 178: 108–117
- 53 Beak J Y, Huang W, Parker J S, et al. An oral selective α -1a adrenergic receptor agonist prevents doxorubicin cardiotoxicity. *JACC Basic Transl Sci*, 2017, 2: 39–53
- 54 Henninger C, Huelsenbeck S, Wenzel P, et al. Chronic heart damage following doxorubicin treatment is alleviated by lovastatin. *Pharmacol Res*, 2015, 91: 47–56
- 55 Santos D L, Moreno A J M, Leino R L, et al. Carvedilol protects against doxorubicin-induced mitochondrial cardiomyopathy. *Toxicol Appl Pharmacol*, 2002, 185: 218–227
- 56 Oliveira P J, Bjork J A, Santos M S, et al. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. *Toxicol Appl Pharmacol*, 2004, 200: 159–168
- 57 Reichardt P, Tabone M D, Mora J, et al. Risk-benefit of dexrazoxane for preventing anthracycline-related cardiotoxicity: re-evaluating the European labeling. *Future Oncol*, 2018, 14: 2663–2676
- 58 Wang X, Wang Q, Li W, et al. TFEB-NF- κ B inflammatory signaling axis: a novel therapeutic pathway of dihydrotanshinone I in doxorubicin-induced cardiotoxicity. *J Exp Clin Cancer Res*, 2020, 39: 93
- 59 Wang X, Sun Q, Jiang Q, et al. Cryptotanshinone ameliorates doxorubicin-induced cardiotoxicity by targeting Akt-GSK-3 β -mPTP pathway in vitro. *Molecules*, 2021, 26: 1460
- 60 Shi Y, Li F, Shen M, et al. Luteolin prevents cardiac dysfunction and improves the chemotherapeutic efficacy of doxorubicin in breast cancer. *Front Cardiovasc Med*, 2021, 8: 750186
- 61 Zhang Y D, Ma C Y, Liu C S, et al. Luteolin attenuates doxorubicin-induced cardiotoxicity by modulating the PHLPP1/AKT/Bcl-2 signalling pathway. *PeerJ*, 2020, 8: e8845
- 62 Lu J, Li J, Hu Y, et al. Chrysophanol protects against doxorubicin-induced cardiotoxicity by suppressing cellular PARylation. *Acta Pharm Sin B*, 2019, 9: 782–793
- 63 Yoon C S, Kim H K, Mishchenko N P, et al. Spinochrome D attenuates doxorubicin-induced cardiomyocyte death via improving glutathione metabolism and attenuating oxidative stress. *Mar Drugs*, 2019, 17: 2
- 64 Liu D, Ma Z, Xu L, et al. PGC1 α activation by pterostilbene ameliorates acute doxorubicin cardiotoxicity by reducing oxidative stress via enhancing AMPK and SIRT1 cascades. *Aging*, 2019, 11: 10061–10073
- 65 Su S, Li Q, Liu Y, et al. Sesamin ameliorates doxorubicin-induced cardiotoxicity: involvement of Sirt1 and Mn-SOD pathway. *Toxicol Lett*, 2014, 224: 257–263
- 66 Jain A, Rani V. Assessment of herb-drug synergy to combat doxorubicin induced cardiotoxicity. *Life Sci*, 2018, 205: 97–106
- 67 Timm K N, Tyler D J. The role of AMPK activation for cardioprotection in doxorubicin-induced cardiotoxicity. *Cardiovasc Drugs Ther*, 2020, 34: 255–269

Molecular mechanisms of doxorubicin-induced cardiotoxicity based on mitochondrial function and traditional Chinese medicine treatment

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Doxorubicin (DOX), an anthracycline chemotherapeutic drug, is one of the most effective drugs for the treatment of various cancers. However, its therapeutic effect is seriously limited by related cardiotoxicity. Although this field has yielded many studies, the exact molecular mechanism of DOX-induced cardiotoxicity (DIC) is still worthy of further study. DOX is a mitochondrial toxin, and mitochondrial damage is the core of DIC. This paper reviews a large amount of literature and summarizes the mechanisms related to DIC that depend on mitochondrial dysfunction, including the effects of DOX on mitochondrial electron transport chain, redox cycle, oxidative stress, calcium imbalance, apoptosis pathway and mitophagy. In addition, it discusses the existing strategies of traditional Chinese medicine based on mitochondrial function to prevent and/or reduce DIC, to provide a scientific basis for combination of DOX and traditional Chinese medicine in the treatment of cancer.

doxorubicin, cardiotoxicity, mitochondrial function, traditional Chinese medicine

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