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◇综述◇

NOD样受体蛋白3炎症小体在多柔比星诱导心脏毒性中的意义

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摘要 晚期肿瘤病人的生命周期因新药的出现不断延长,同时,抗肿瘤药物所致的毒副作用也受到重视。多柔比星(DOX)作为强大的广谱抗肿瘤药物虽极大地延长了肿瘤病人的生存周期,但其诱导的剂量相关性的心脏毒性限制了其临床应用。NOD样受体蛋白3(NLRP3)炎症小体在DOX诱导的心脏毒性(DIC)的炎症过程发挥着重要作用,且一些炎症小体抑制剂还可减轻DIC。该文根据近5年的最新进展,围绕NLRP3炎症小体参与DIC的作用及机制等做一归纳、总结。

关键词 多柔比星; NOD样受体蛋白3; 心脏毒性

Significance of NLRP3 inflammasome in doxorubicin-induced cardiactoxicity

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Abstract The life cycle of patients with advanced tumors has been prolonged due to the emergence of new drugs, while meanwhile the side effects of anti-tumor drugs have also been paid attention to. Doxorubicin (DOX), as a powerful broad-spectrum anti-tumor drug, has greatly prolonged the life cycle of tumor patients, but its clinical application is limited by dose-dependent cardiotoxicity. NOD like receptor protein 3 (NLRP3) inflammasome plays an important role in the inflammatory process of DOX-induced cardiotoxicity (DIC), and some inhibitors of inflammasome can reduce DIC. Based on the latest research progress in the past 5 years, this article summarized how the NLRP3 inflammasome involves in DIC.

Keywords Doxorubicin; NOD-like receptor protein 3; Cardiotoxicity

手术、放化疗、靶向治疗、免疫治疗等治疗方式使恶性肿瘤治疗取得了长足的进步,肿瘤病人的生存期也得到大幅延长。多柔比星(doxorubicin,DOX)是一种广谱的蒽环类抗生素。在抗肿瘤的同时也可导致剂量依赖性的心脏毒性,最终可能发展为充血性心力衰竭和死亡[1]。此外,DOX使用周期长和年龄(如儿童)、糖尿病或心血管疾病(如高血压、高血脂或动脉粥样硬化)等更易导致这些并发症,吸烟、肥胖或不运动也会增加心脏毒性风险[2]。因此,仍然迫切需要确定新的药理靶点,以减轻多柔比星诱导心脏毒性(doxorubicin-induced cardiotoxicity, DIC)作用。作为感染和外部刺激的传感器,含有NOD样受体蛋白3(NOD-like receptor protein 3, NLRP3)炎症小体的核苷酸结合寡聚化结构域(NOD)样受体家族pyrin结构域在各种疾病的病理过程中起着关键作用。有趣的是,降低NLRP3炎症小体的活性可减轻DIC。因此,针对这一发现,我们回顾并梳理了目前关于NLRP3炎症小体在DIC中潜在意义的研究。

1 NLRP3炎症小体结构与功能

NLRP3是一种模式识别受体(pattern recognition receptor, PRR),识别细菌和病毒性病原体相关分子模式(pathogen-associated molecular patterns, PAMPs),但也识别与组织和细胞损伤有关的多种危险相关分子模式(damage-associated molecular patterns, DAMPs)。PAMP或DAMP,或细胞因子如肿瘤坏死因子(tumournecrosis factor,TNF)和白细胞介素-1β(interleukin-1β, IL-1β)可识别PRR如Toll样受体(toll-like receptor,TLR)、白细胞介素-1受体(interleukin-1 receptor, IL-1R)激活炎症小体[3]。

NLPR3炎症小体的激活需要两个阶段，首先，DAMPs或PAMPs识别TLR，激活核因子κB（nuclear factor kappa-B，NF-κB）通路，导致NLRP3和白细胞介素-1β前体（pro-Interleukin-1β，pro-IL-1β）和pro-IL-18的产生。其次，由NLRP3蛋白、凋亡相关斑点样蛋白（apoptosis- associated speck- like protein containing a CARD，ASC），和胱天蛋白酶-1的前体（pro-caspase-1）组成NLRP3炎症小体，使pro-caspase-1切割成活性形式的caspase-1，进而pro-IL-1β和pro-IL-18形成生物活性IL-1β和IL-18，诱导炎症反应[4]。激活的Caspase-1识别和切割引起GSDMD激活并在细胞膜中形成GSDMD通道，引起细胞凋亡[5]。线粒体功能障碍及活性氧（reactive oxygen species，ROS）的产生，胞质钙超载、钾外流、氧化应激（oxidative stress，OS）和溶酶体损伤等均可诱导NLRP3炎症小体的激活和组装[6]。

2 NLRP3炎症小体在DIC中的作用

DOX是一类抗癌药物，用于白血病、淋巴瘤、膀胱癌、乳腺癌、小细胞肺癌和其他实体瘤等多种癌症的治疗。DOX可插入DNA双螺旋的碱基抑制DNA和RNA的合成，也可与DNA反应并引发细胞凋亡。目前，研究人员认为DIC的原因主要与线粒体功能障碍、ROS产生、OS、炎症反应、细胞焦亡等相关[7-8]。因心肌细胞富含线粒体，缺乏抗氧化酶，可产生大量ROS，ROS可激活NLRP3及后续因子的释放，更易使心脏产生毒副作用。另一些研究证明，15 mg/kg的DOX足以建立心脏毒性小鼠模型[9]。NLRP3炎症小体的活性被抑制改善了DOX诱导小鼠或大鼠的左心室收缩功能障碍和心肌细胞死亡[10-11]。强调了NLRP3炎症小体在DIC中的重要作用。

NLRP3炎症小体激活的两个阶段：（1）DAMPs或PAMPs结合细胞膜上TLR，激活NF-κB通路，导致NLRP3、pro-IL-1和pro-IL-18的产生或激活。（2）组装（NLRP3、ASC、pro-caspase-1）成NLRP3炎症小体，进而pro-caspase-1转化成生物活性形式的caspase-1，促进pro-IL-1β和pro-IL-18，形成成熟体IL-1β和IL-18，诱导炎症反应。激活：线粒体功能障碍及ROS的产生、胞质钙超载、钾外流、OS和溶酶体损伤、DAMPs或PAMPs、IL-1β等。

NLRP3炎症小体是一个复杂的调节蛋白网络，可启动炎症反应，越来越多的证据表明，在DIC的发展中，NLRP3炎症小体的激活及后续炎症细胞因子的分泌起着核心作用。例如，Zhu等[12]对小鼠腹腔注射DOX后发现，空泡化心肌细胞显著增多及肌原纤维紊乱，这两者都是心脏损伤的标志。同时，检测血清和心脏组织中IL-1β水平显著增加，并呈剂量依赖性，推测IL-1信号可能部分参与DOX诱导的急性心脏损伤[12]。同样，Sauter等[13]在ASC、caspase-1或NLRP3缺陷的小鼠骨髓源性巨噬细胞中，DOX未能诱导IL-1β的释放，这表明DOX诱导的炎症是由NLRP3炎症小体介导的。另外研究表明，DOX还可通过诱导TINCR（terminal differentiation-induced lnc RNA，TINCR）基因启动子区的H3K27乙酰化并激活心肌细胞中的转录，增加了TINCR的表达。通过胰岛素样生长因子Ⅱ mRNA结合蛋白1（IGF2BP1）增加mRNA的稳定性，增强TINCR上调NLRP3的表达的作用，激活caspase-1和GSDMD途径[14]。MCC950（NLRP3抑制剂）可使DOX诱导小鼠和H9c2细胞中NLRP3、ASC、caspase-1、IL-1β、IL-18和GSDMD的表达水平降低，进而抑制细胞凋亡[15]。因此，DOX诱导的心脏损伤与NLRP3炎症小体活化存在相关性。

机制上，ROS可激活NLRP3炎症小体。线粒体功能障碍可使ROS产生增加，Catanzaro等[16]发现，线粒体内DOX的浓度达到50~100 μmol/L时，可使ROS产生增加。同样，在DOX诱导的扩张性心肌病模型小鼠中，经DOX治疗可激活调控动力相关蛋白1进而上调NOX1［烟酰胺腺嘌呤二核苷酸磷酸（NADPH）氧化酶1］和NOX4的表达，诱导线粒体分裂，ROS积聚，导致NLRP3炎症小体通过caspase-1依赖性方式介导心肌细胞焦亡[17]。另一项研究也表明，DOX诱导小鼠心肌和心肌细胞凋亡，同时ROS过度产生，NLRP3、ASC和caspase-1 p20表达上调，以及心肌细胞中IL-1β分泌增加[18]。此外，核因子红细胞2相关因子2（nuclear factor erythroid 2-related factor 2，Nrf2）是参与细胞对ROS反应的重要信号分子。DOX可以通过激活Nrf2信号通路以上调P-gp表达来增加ROS[19]。并在DOX诱导急性心脏毒性的心肌细胞观察到Nrf2 mRNA和Nrf2蛋白表达水平降低[20]。因此，NOX1、NOX4、Nrf2可通过ROS-NLRP3在DIC中发挥一定的作用。

DOX还被证明通过抑制sirtuin家族的成员来干扰线粒体功能，sirtuiin家族催化组蛋白和非组蛋白赖氨酸残基的脱乙酰化。DOX治疗可以抑制小鼠心脏以及H9c2和原代心肌细胞中SIRT3的表达[21]。SIRT3的过度表达减少了ROS水平，保护了线粒体功能，并保护线粒体DNA免受DOX治疗的损伤[[22]。SIRT1是另一个sirtuin家族成员，一种烟酰胺腺嘌呤二核苷酸依赖性的Ⅲ类组蛋白去乙酰化酶，通过增强自噬和减少因缺氧诱导的细胞凋亡，对心肌细胞发挥保护作用[23]。DOX抑制SIRT1的表达。

SIRT1缺失会加重DOX诱导的细胞毒性,并破坏线粒体功能[24]。而SIRT1的过度表达抑制DOX诱发的细胞凋亡和ROS产生[25]。DOX下调H9c2细胞和小鼠心脏组织中的SIRT1表达并激活NLRP3炎症小体和增加硫氧还蛋白相互作用蛋白(thioredoxin interacting protein, TXNIP)水平,促进心肌细胞凋亡[26]。此外,DOX诱导的H9c2心肌细胞衰老依赖于硫氧还蛋白相互作用蛋白(TXNIP)/NLRP3炎症小体途径[27]。总之,sirtuins可以调节线粒体功能,从而促进心肌细胞存活。这些实验确定了sirtuin作为DOX诱导的心脏毒性的潜在治疗靶点。

丝氨酸/苏氨酸蛋白激酶(mitogen-activated protein kinase, MAPK)具有调节细胞增殖、分化、凋亡等作用,由p38 MAPK丝裂原活化蛋白激酶(p38 Mitogen-activated protein kinases, p38 MAPK)、c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)和细胞外调节蛋白激酶(extracellular signal regulated kinase, ERK)组成。DOX治疗显著增加了小鼠TLR4、NLRP3、caspase-1、IL-1β、IL-18、TNF-α和细胞信号蛋白(MyD88、p-P38和p-JNK)的心脏表达[28]。在髓样分化蛋白1(MD-1)基因敲除小鼠中,Zhang等[29]观察到,DOX可加速心功能障碍和心肌损伤、促进细胞凋亡,可能通过激活TLR4/MAPKs/NF-κB途径实现的。因此,DOX还可作用于TLR4/MAPKs进而导致NLRP3激活致心脏损伤。尽管有令人信服的证据表明,在DOX处理的小鼠中,抑制NLRP3炎症小体的激活具有心脏保护作用,但独立于炎症小体NLRP3活性也可能是对DOX的保护作用的原因[30]。

总之,NLRP3炎症小体通过诱导心肌细胞凋亡、焦亡和心肌炎症反应参与DIC的发生和发展,但具体机制目前尚不清楚。

3 抑制NLRP3对DIC防治的作用研究

近年来,有很多研究者发现使用某些天然化合物、药物、其他等可通过靶向多种途径中的一种或多种途径抑制NLRP3炎症小体的激活,减轻DIC。见表1。

综上所述,大量研究证实了NLRP3炎症小体在DOX治疗引起细胞死亡和炎症反应中所起的核心作用。DOX诱导的心脏炎症涉及多种途径,NLRP3的过度表达加重了DOX诱导的心脏损伤。同时,NLRP3炎症小体的下调有效地预防了DOX引发的心脏毒性。因此,抑制NLRP3炎症小体激活可能是防止DIC的有效方法。然而,上述研究大多在细胞和动物模型上开展,缺少在人体内的研究,更缺乏临床随机对照试验的研究加以支持。此外,天然化合物、药物、其他等虽可改善DIC,但是我们期待临床试验进一步证实临床效果,寻找可为临床使用的易于获取的能抑制NLRP3炎症小体的抗炎药物,从而改善DIC病人的预后。

表1 关于天然化合物、药物、其他等通过抑制NLRP3炎症小体激活治疗DIC的总结

种类	模型	靶点	生物效应	引用文献
白杨素	DIC大鼠	MAPK/NF-κB、iNOS、COX-2、TNF-α	OS、炎症、细胞焦亡↓	[31-32]
橙花叔醇	DIC大鼠	NF-kB/MAPK	线粒体功能障碍、DNA损伤、细胞凋亡↓	[33]
小豆蔻明	DIC小鼠、H9C2细胞、HL-1细胞	Nrf2/NF-κB	OS、炎症、细胞焦亡↓	[34]
甘草素	DIC小鼠	MAPK/NF-κB	OS、炎症、细胞焦亡↓	[35]
白藜芦醇	DIC大鼠、DIC小鼠	TLR4/NF-kB/MAPK、NLRP3	OS、炎症↓	[36-37]
毛蕊异黄酮	DIC小鼠、H9C2细胞、DIC小鼠	SIRT1/TXNIP/NLRP3 NLRP3-caspase-1-GSDMD	OS、线粒体功能障碍、细胞焦亡↓	[26, 38]
和厚朴酚	H9C2细胞	TXNIP/NLRP3、AMPK/Nrf2	细胞衰老↓、细胞焦亡↓	[27, 39]
姜黄素	DIC小鼠	mTOR、NLRP3	细胞凋亡↓、自噬↑	[40]
二氢杨梅素	DIC大鼠	SIRT1-NLPR3	炎症↓	[11]
生松素	DIC小鼠	Nrf2/SIRT3-NLRP3	细胞凋亡↓	[41]
秦皮素	DIC大鼠	ROS-NLRP3	OS、细胞凋亡↓自噬↑	[42]
右美托咪定	H9C2细胞	TXNIP、NLRP3、ASC、caspase-1	细胞凋亡↓	[43]
恩格列净	DIC小鼠、HL-1细胞	NLRP3、MyD88	铁死亡、炎症、细胞凋亡↓	[44]
烟酰胺单核苷酸	DIC大鼠	ROS-NLRP3	细胞凋亡↓	[45]
硒	DIC小鼠	Nrf2-NLRP3	OS、炎症↓	[46]
lncRNA-TINCR	DIC大鼠、H9C2细胞	TINCR/IGF2BP1/NLRP3	细胞凋亡↓	[14]
热休克蛋白22	DIC小鼠	TLR4/NLRP3	细胞凋亡↓	[47]
消退素E1	人脐静脉内皮细胞、CFs	NLRP3、IL-1β	细胞衰老↓、CFs↓	[48-49]
胚胎干细胞衍生的外泌体	DIC小鼠、H9C2细胞	TLR4/NLRP3	炎症、细胞凋亡↓	[28, 50]

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