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有氧运动抑制炎症反应改善动脉粥样硬化小鼠心肌细胞凋亡的机制研究

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[摘要] **目的**:探讨有氧运动抑制炎症反应对动脉粥样硬化小鼠心肌细胞凋亡的影响及机制。**方法**:选取8周龄雄性$ApoE^{-/-}$基因敲除小鼠,适应性饲喂1周后,随机分为对照组、模型组和有氧运动组,每组9只;模型组和有氧运动组饲以"西方类型"膳食饲料喂养12周,建立动脉粥样硬化模型,有氧运动组同时进行有氧训练。12周后TUNEL染色检测小鼠的心肌细胞凋亡情况,免疫组化检测各组NOD样受体热蛋白结构域相关蛋白3(NLRP3)、白细胞介素-1β(IL-1β)和转化生长因子-β1(TGF-β1)的表达,Western blot检测NLRP3、IL-1β和TGF-β1的蛋白水平。试剂盒检测小鼠血清中乳酸脱氢酶(LDH)、肌酸激酶(CK)的活性,ELISA检测血清中心肌肌钙蛋白I(cTnⅠ)的水平。**结果**:TUNEL染色显示3组小鼠在心肌细胞凋亡间的差异均具有统计学意义($P<0.01$)。同时免疫组化显示模型组心肌组织NLRP3、IL-1β、TGF-β1蛋白表达量高于对照组和有氧运动组($P<0.05$)。Western blot显示模型组和有氧运动组心肌组织中NLRP3、IL-1β和TGF-β1蛋白水平的含量显著高于对照组($P<0.01$);与模型组相比,有氧运动组心肌组织中NLRP3、IL-1β和TGF-β1蛋白水平的含量均显著降低($P<0.001$)。三组在LDH、CK和cTnⅠ间的差异均具有统计学意义($P<0.01$)。**结论**:有氧运动能够改善动脉粥样硬化小鼠心肌细胞凋亡,其机制可能与有氧运动抑制小鼠心肌组织炎症反应及降低心肌酶水平有关。

[关键词] 有氧运动;动脉粥样硬化;心肌酶;炎症;凋亡
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Aerobic exercise inhibits inflammatory response to improve apoptosis in atherosclerotic mice cardiomyocytes

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View from specialist: It is creative, and of certain scientific and educational value.

[Abstract] **Objective**: To investigate the effects and mechanisms of aerobic exercise to inhibit inflammatory response on cardiomyocyte apoptosis in atherosclerotic mice. **Methods**: Male $ApoE^{-/-}$ knockout mice were selected at 8 weeks of age, and after 1 week of adaptive feeding, they were randomly divided into a control group, a model group and an aerobic exercise group, with 9 mice in each group; model group and aerobic exercise group were fed with "Western-type" dietary feeds for 12 weeks to establish an atherosclerosis model, while the aerobic exercise group underwent aerobic training at the same time. After 12 weeks, the cardiomyocyte apoptosis was detected in mice by TUNEL staining. The expression of NOD-like receptor protein 3 (NLRP3), interleukin-1β (IL-1β) and transforming growth factor-β1 (TGF-β1) were detected by immunohistochemistry in each group. The protein

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levels of NLRP3, IL-1β and TGF-β1 were detected by Western blot. The kit detects the activity of lactate dehydrogenase (LDH) and creatine kinase (CK) in mice serum, and ELISA detects the level of cardiac troponin I (cTnⅠ) in serum. **Results**: TUNEL staining showed that there were statistically differences in cardiomyocyte apoptosis among the three groups ($P<0.01$); meanwhile, immunohistochemistry showed that the expression of NLRP3, IL-1β and TGF-β1 protein in myocardial tissue of the model group was higher than that of the control group and the aerobic exercise group ($P<0.05$). Western blot showed that the levels of NLRP3, IL-1β and TGF-β1 protein in the myocardial tissue of the model group and the aerobic exercise group were significantly higher than those in the control group ($P<0.01$). Compared with the model group, the levels of NLRP3, IL-1β and TGF-β1 protein in the myocardial tissue of the aerobic exercise group were significantly decreased ($P<0.001$). The differences between the three groups in LDH, CK and cTnⅠ were statistically significant ($P<0.01$). **Conclusion**: Aerobic exercise can improve cardiomyocyte apoptosis in atherosclerotic mice, and its mechanism may be related to the inhibition of inflammatory response in myocardial tissue and the reduction of myocardial enzyme.

[**Key words**] Aerobic exercise; Atherosclerosis; Cardiac enzymes; Inflammation; Apoptosis

心血管疾病是全球主要死亡原因[1,2],其最常见的危险因素是动脉粥样硬化(atherosclerosis,AS)。AS是一种血管壁慢性炎症性疾病[3],其特征为细胞死亡和炎症因子释放增加。AS疾病的进展会引发心功能改变,导致心肌梗死、冠心病等多种心血管疾病,这一过程涉及炎症反应、氧化应激、巨噬细胞活化、炎症因子的相互作用[4],内皮损伤、脂质沉积和遗传易感性等[5,6]。深入研究AS对心肌细胞的影响及机制对于心血管病的防治具有重要意义。

炎症小体是一组参与多种疾病进展过程中炎症、免疫反应和代谢异常的蛋白复合体[7],NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)炎症小体是目前最具代表性和最容易识别的炎症小体[8]。炎症反应是机体防御感染及修复损伤的保护性反应,但持续存在的慢性炎症与诸多疾病的发生和发展相关[9]。动脉粥样斑块的形成能够造成心肌组织缺血、缺氧损伤,进而促进NLRP3、白细胞介素-1β(Interleukin-1β, IL-1β)、白细胞介素-18(Interleukin 18, IL-18)等炎症因子的过度表达[10,11],诱发心肌损伤和细胞凋亡[12,13]。

有氧运动在一定程度上能够减轻心肌氧化应激和炎症反应[14],减缓损伤,抑制促凋亡因子的表达,改善心肌细胞凋亡[15]。目前研究多集中于有氧运动对心肌梗死、心肌缺血再灌注损伤等疾病的心功能改善,其机制与炎症反应[16]、线粒体自噬[17]、氧化应激和细胞凋亡等有关[18,19]。潘红英等[20]研究表明有氧运动能够激活AMPK、PPARα的表达,改善AS所致心肌能量代谢紊乱与心肌损伤。研究表明游泳能够降低促炎细胞因子TNF-α与心肌损伤标志物的浓度,减轻心肌细胞凋亡保护缺血再灌注大鼠心肌损伤[21]。此外,研究表明运动训练可通过激活AMPK抑制NLRP3炎性小体的激活,从而减轻异丙肾上腺素诱导的野生小鼠心脏炎症[22]。课题组前期研究发现,AS所致小鼠心肌组织存在炎症反应与心肌纤维化加重的现象,而有氧运动能够抑制上述过程。细胞凋亡与心肌纤维化、炎症反应密切相关。心肌组织长期的炎症浸润会导致细胞凋亡增多,细胞凋亡失调会诱导成纤维细胞向肌成纤维细胞转化和细胞外基质过度沉积,诱发纤维化的发生[23]。但有氧运动能否通过抑制NLRP3炎症小体的活化,降低炎症因子分泌,进而抑制AS所致小鼠心肌损伤与细胞凋亡尚未见相关报道。为此,本研究基于动物模型,探讨有氧运动对AS小鼠心肌细胞凋亡的影响,并从心肌细胞炎症反应的角度探讨其机制。

1 材料与方法

1.1 动物饲养及实验方法

选取27只8周龄SPF级雄性$ApoE^{-/-}$基因敲除小鼠为实验研究对象,体重20~24 g,购自中国科学院实验动物中心,许可证号[SCXK(京)2019-0008]。所有小鼠自由饮水和饮食,温度为(22±1)℃,湿度为45%~55%,光照/黑暗周期为12 h。适应性喂养1周后,通过随机数字表分为对照组(control group, CG组)、模型组(atherosclerosis group,AS组)和有氧运动组(aerobic exercise group, AE组),每组9只。参考已有文献,模型组和有氧运动组小鼠饲以"西方类型"膳食饲料(21%脂肪,0.15%胆固醇)喂养12周,建立AS模型[24]。AE组在建模的同时进行有氧训练,AS组不进行有氧训练,CG组正常饮食,不进行任何干预。研究经山东中医药大学附属医院动物伦理委员会审核同意(伦理编号:AWE-2022-004),符合伦理规范要求。

1.2 运动训练方案

AE组令小鼠在小动物活动跑台上进行递增运动强度和时间的耐力性运动。参考基因缺陷小鼠的运动标准[25],采用逐渐递增运动强度和时间的跑台运动,运动由第1~4周10 m/min,30 min/d,逐渐

增加至13 m/min，60 min/d，自第5周开始为稳定的运动量13 m/min，60 min/d。每周运动5次，与建模同时进行，连续运动12周。CG组和AS组不进行训练。

1.3 主要试剂与仪器

BCA蛋白浓度测定试剂盒（WLA004，万类生物），超速冷冻离心机（H-2050R，湖南湘仪），显微镜（BX53，OLYMPUS公司，日本），显微镜拍照系统（OLYMPUS公司，日本），NLRP3 antibody（WLH3383-1，万类生物），IL-1β antibody（WLH3903-1，万类生物），TGF-β1 antibody（WL02193，万类生物），羊抗兔IgG-HRP（WLA023，万类生物），TUNEL试剂盒（WLA029b，万类生物），内参抗体β-actin（WL01372，万类生物），肌酸激酶（CK）测试盒（A032，南京建成），乳酸脱氢酶（LDH）测定试剂盒（WLA072b，万类生物），Mouse CTnⅠ ELISA Kit（EM1466，武汉菲恩）。

1.4 小鼠主动脉苏丹Ⅳ染色

小鼠处死后，固定于手术台上，剪开胸腔，暴露心脏，小心分离胸腹主动脉至髂动脉分支，仔细剥离动脉周边的结缔组织，纵向剖开动脉PBS清洗，将主动脉置于Herherimers液（苏丹Ⅳ 5 g，70%酒精500 mL，丙酮50 mL混匀）中浸泡20 min，80%酒精分色20 min，流水冲洗1 h。

1.5 小鼠心肌组织TUNEL染色

取心肌组织多聚甲醛固定后石蜡包埋切片，依次放入二甲苯、无水乙醇、不同浓度的乙醇中浸泡，按TUNEL试剂盒说明进行操作。TUNEL染色阳性的凋亡细胞呈绿色荧光。

1.6 免疫组化

心肌组织切片，依次在二甲苯、无水乙醇和95%、85%和75%的乙醇中脱蜡至水，抗原修复，孵育，封闭，加入1∶100稀释的一抗，4 ℃过夜，洗涤5分钟重复3次，再加入1∶500稀释的HRP标记山羊抗兔IgG抗体，孵育，后进行DAB染色、苏木素染液复染、盐酸乙醇分化、流水返蓝操作，脱水，透明，取出切片，滴加中性树胶，盖玻片封片，室温晾干。显微镜下观察染色效果，Image J计算平均光密度值并进行统计分析。

1.7 Western blot检测

取小鼠新鲜心肌组织，快速冰冻后匀浆，加入RIPA裂解液充分混匀，BCA法测定蛋白浓度。配制5%浓缩胶，10%、15%分离胶，电泳，湿转法转膜1.5 h，5%的脱脂奶粉室温封闭1 h，加入稀释后的一抗，抗NLRP3（1∶500稀释）、抗IL-1β（1∶1 000稀释）、抗TGF-β1（1∶400稀释），4 ℃孵育过夜，洗膜，加入二抗，室温孵育，以β-actin为内参，洗膜后加入ECL发光试剂，曝光成像。

1.8 试剂盒检测心肌酶含量

使用测试盒检测小鼠血清中CK和LDH的含量。按照试剂盒说明进行操作于波长660 nm，1 cm光径比色，测定各管吸光度值，计算CK活力。于波长450 nm，酶标仪测定吸光度值，计算LDH活性。

1.9 ELISA检测cTnⅠ含量

配制标准品溶液并进行2倍倍比稀释，在96孔板中加入稀释后的标准品溶液和血清，按照说明书依次进行孵育、洗涤、加入生物素标记抗体孵育、洗涤、加入HRP标记山羊抗兔IgG孵育、洗涤、加入TMB底物，最后加入停止液后，立即在450 nm处用酶标仪读取吸光度值，根据浓度和吸光度值绘制标准曲线并分析。

1.10 统计学处理

数据分析采用SPSS26.0软件，定量数据采用（$\bar{x}\pm s$）或$M(P_{25},P_{75})$数表示，符合正态分布的，组间比较采用方差分析，两两比较采用LSD检验；不符合正态分布的，组间比较采用Wilcoxon非参数检验。$P<0.05$为差异具有统计学意义。

2 结果

2.1 小鼠主动脉苏丹Ⅳ染色

CG组无明显染色，AS组脂肪染色明显，小鼠主动脉血管出现脂质病变，说明模型构建成功，AE组脂肪染色较AS组明显减轻，有氧运动可改善主动脉血管脂质病变。见图1。

2.2 Tunel染色检测心肌细胞凋亡

Tunel染色显示，CG组可见少量呈绿色荧光的凋亡心肌细胞，小鼠心肌细胞凋亡状况明显低于AS组和AE组（$P<0.001$），而AE组相较于AS组绿色荧光点明显减少，心肌凋亡状况较显著改善（$P<0.01$）。见图2及表1。

2.3 免疫组化检测小鼠心肌组织NLRP3、IL-1β、TGF-β1的表达

免疫组化检测各组小鼠心肌组织中的NLRP3、IL-1β、TGF-β1结果显示，AS组小鼠心肌组织NLRP3、IL-1β、TGF-β1蛋白表达比CG组增多（$P<0.01$），而AE组小鼠心肌组织NLRP3、IL-1β、TGF-β1表达量较AS组降低（$P<0.05$）。见图3及表2。

2.4 Western blot检测小鼠心肌组织中NLRP3、IL-1β、TGF-β1

Western blot检测结果显示，各组小鼠总体差异有统计学意义（F分别为355.470、205.589、215.450，

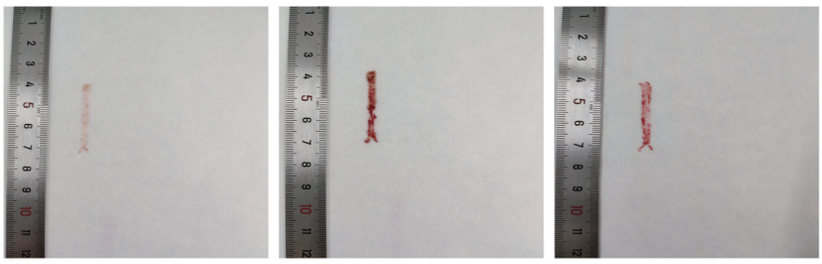
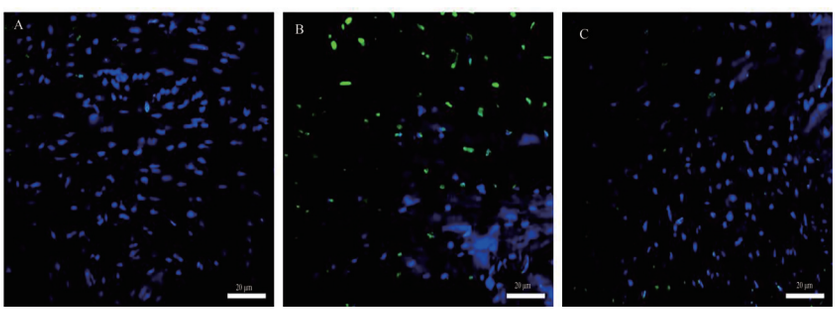


图1 小鼠主动脉苏丹Ⅳ染色

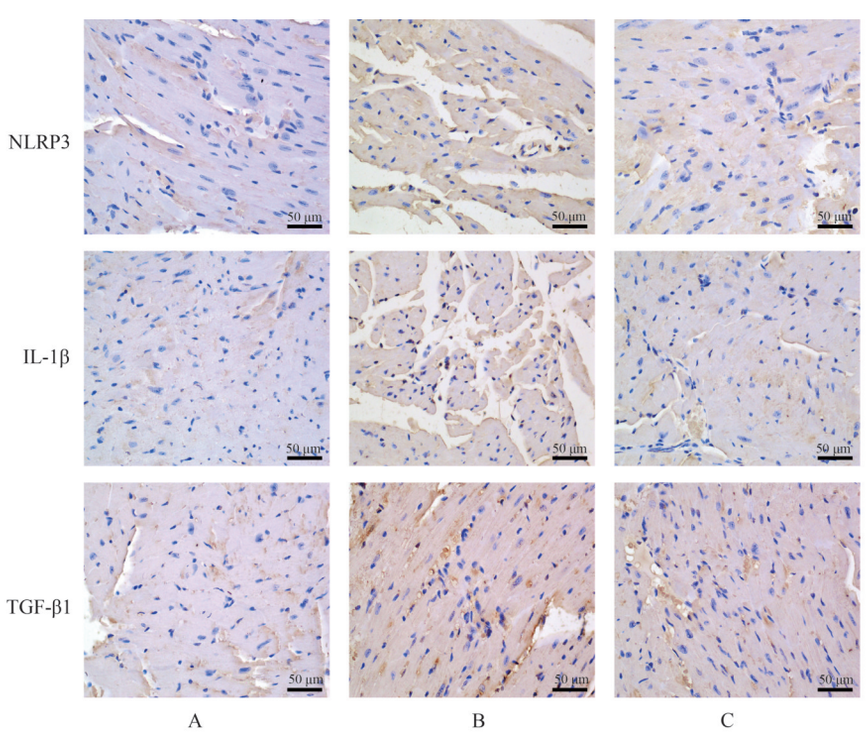
Fig 1 Sudan Ⅳ staining of mouse aorta



A:CG;B:AS;C:AE

图2 各组小鼠心肌细胞凋亡Tunel染色结果(×400,标尺=20 μm)

Fig 2 Tunel staining in each group (×400, scale bar=20 μm)

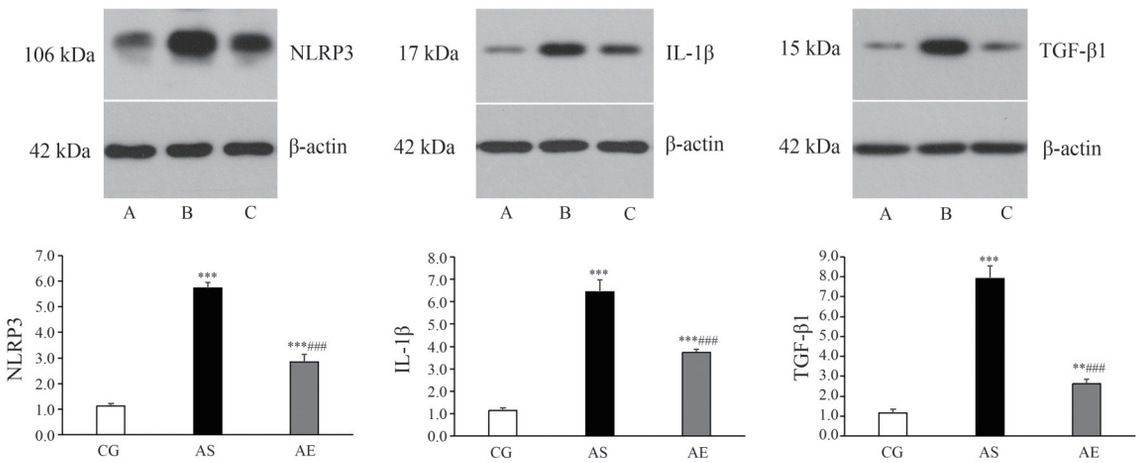


A: CG; B: AS; C: AE

图3 小鼠心肌组织中的免疫组化检测结果(×400,标尺=50 μm)

Fig 3 The results of immunohistochemical detection of NLRP3、IL-1β and TGF-β1 in myocardial tissue(×400,scale bar=50 μm)

$P<0.01$),AS组和AE组心肌组织中NLRP3、IL-1β和TGF-β1蛋白水平的含量显著高于CG组($P<0.01$);与AS组相比,AE组心肌组织中NLRP3、IL-1β和TGF-β1蛋白水平的含量均显著降低($P<$



A:CG;B:AS;C:AE;n=3,与CG组比较,$^{**}P<0.01$,$^{***}P<0.001$;与AS组比较,$^{\#\#\#}P<0.001$

图4　心肌组织中NLRP3、IL-1β、TGF-β1蛋白水平Western blot检测结果

Fig 4　The protein levels of NLRP3, IL-1β and TGF-β1 in myocardial tissue detected by Western blot

表1　各组小鼠心肌细胞凋亡率的比较($\bar{x}\pm s$, n=3)

Tab 1　Comparison of cardiomyocyte apoptosis rate in each group of mice($\bar{x}\pm s$, n=3)

组别	细胞凋亡率(%)
CG组	6.84±0.81
AS组	30.11±3.49***
AE组	21.30±2.73***##
F	61.373
P	0.000

注:与CG组比较,$^{***}P<0.001$;与AS组比较,$^{\#\#}P<0.01$。

表2　各组小鼠心肌组织免疫组化NLRP3、IL-1β和TGF-β1表达比较($\bar{x}\pm s$, n=3)

Tab 2　The expression of NLRP3, IL-1β and TGF-β1 in myocardial tissue of mice in each group was compared by immunohistochemistry($\bar{x}\pm s$, n=3)

组别	NLRP3	IL-1β	TGF-β1
CG组	0.06±0.01	0.06±0.01	0.06±0.01
AS组	0.10±0.01**	0.10±0.01**	0.11±0.01**
AE组	0.08±0.01#	0.08±0.01#	0.08±0.01#
F	9.903	11.315	11.927
P	0.013	0.009	0.008

注:与CG组比较,$^{**}P<0.01$;与AS组比较,$^{\#}P<0.05$。

0.001)。见图4。

2.5　各组LDH、CK和cTnⅠ的比较

方差分析显示,3组在LDH、CK和cTnⅠ间的差异均具有统计学意义($P<0.01$),与CG组相比,AS组、AE组LDH、CK和cTnⅠ水平均显著升高($P<0.01$),但AE组LDH、CK和cTnⅠ水平显著低于AS组($P<0.01$)。见表3。

表3　各组LDH、CK和cTnⅠ的检测结果($\bar{x}\pm s$, n=3)

Tab 3　The levels of LDH、CK and cTnⅠ in myocardial tissue of mice in each group($\bar{x}\pm s$, n=3)

组别	LDH(U/L)	CK(U/mL)	cTnⅠ(pg/mL)
CG组	227.45±8.99	0.44±0.03	98.17±1.37
AS组	413.73±26.53***	0.80±0.02***	202.90±1.06***
AE组	303.92±32.40**##	0.59±0.01***###	140.74±1.76***###
F	43.025	196.855	4 087.057
P	0.000	0.000	0.000

注:与CG组比较,$^{**}P<0.01$,$^{***}P<0.001$;与AS组比较,$^{\#\#}P<0.01$,$^{\#\#\#}P<0.001$。

3　讨论

炎性小体在先天免疫反应和抗感染免疫反应中发挥重要作用,但其过度激活会参与慢性炎症性疾病的发生、发展[26]。NLRP3炎症小体是一种多蛋白复合物,该复合物由NLRP3、细胞凋亡相关的斑点样蛋白和半胱天冬酶-1前体组成[27]。大量研究证实NLRP3炎症小体参与心肌病、心律失常、心肌缺血再灌注损伤等心血管疾病的发生、发展[28-30]。氧化应激、高血糖、血脂异常、炎症、线粒体功能障碍和内质网应激等危险因素可部分激活NLRP3炎症小体[10,31,32]。NLRP3炎症小体激活能够促进下游IL-1β、IL-18等促炎细胞因子的分泌和累积。相关研究表明,有氧运动能够下调NLRP3、caspase-1、IL-1β水平,改善心肌重塑[33,34]。在本研究中,AS小鼠NLRP3炎症小体表达增加,增强了IL-1β促炎细胞因子的下游产生,这有助于AS小鼠细胞凋亡的发生。而有氧运动显著降低NLRP3炎症小体的表

达,下调下游炎症介质IL-1β的产生,减轻小鼠AS进程中心肌细胞炎症反应,与上述研究一致。此外笔者发现有氧运动能够减轻AS小鼠主动脉血管脂质病变,与Chen等[33]研究一致。

长期的炎症浸润能够加重心肌损伤,有氧运动能够减少心脏组织的损伤与炎症浸润[34]。CK、LDH和cTnⅠ的释放量能够反应心肌细胞损伤程度[35-37]。研究表明长期有氧运动在抑制心肌梗死后缺血再灌注大鼠心肌细胞凋亡、改善缺血心脏病心肌损伤等方面发挥着重要作用[38,39]。与上述研究一致,笔者发现有氧运动能够减少AS小鼠心肌细胞凋亡,降低心肌组织CK、LDH和cTnⅠ水平,发挥对心脏的保护作用。

IL-1β是炎症性疾病的重要介质[10],IL-1β能够促进其他促炎细胞因子的合成、激活促纤维化通路、促进心肌细胞凋亡与损伤[40],诱发心肌梗死[26,41]。相关研究表明抑制NLRP3炎症小体和IL-1β的分泌能够降低血清LDH水平,减轻心肌细胞损伤[42,43]。在急性心肌梗死模型中,抗IL-1β血小板微粒能够通过减弱IL-1β及其下游caspase-3的活性抑制心室扩张与心肌细胞凋亡[41]。与上述研究相似,笔者发现有氧运动降低AS小鼠NLRP3和IL-1β水平,减轻细胞凋亡,降低心肌损伤标志物CK、LDH和cTnⅠ的释放。这可能与有氧运动抑制NLRP3炎症小体激活,减少下游炎症因子IL-1β分泌,进而减轻心肌细胞凋亡有关。值得注意的是,Oláh等[44]研究表明有氧运动可使力竭健康大鼠的心肌细胞发生凋亡、Ca^{2+}处理下降[45]、导致心肌细胞功能障碍。这提醒在进行运动训练时需注意运动时间与强度。

AS小鼠心肌缺血缺氧可诱导活性氧的大量产生,导致氧化应激损伤,心肌细胞坏死和凋亡。心肌组织损伤初期会通过细胞外基质重塑来愈合伤口修复受损组织,促使成纤维细胞转化为肌成纤维细胞,转化生长因子β1(transforming growth factor-β1,TGF-β1)与上述过程密切相关。TGF-β1的激活可调节多种细胞功能,包括增殖、分化、凋亡、炎症反应、纤维化。但持续的损伤会导致ECM过度沉积,炎症反应加剧。NLRP3炎症小体炎症会激活炎性因子IL-1β,后者可调控TGF-β1生成,加速心肌细胞凋亡[46]。TGF-β1在心肌细胞凋亡与损伤中具有重要意义,相关研究表明运动训练能够降低心肌纤维化小鼠TGF-β1分泌[47],抑制TGF-β1/Smad3通路的激活,减轻心力衰竭大鼠的心肌细胞凋亡[48]。本实验结果表明,AE组小鼠心肌组织中TGF-β1水平较AS组显著下降,心肌细胞凋亡显著减轻,这表明有氧运动能够抑制TGF-β1分泌,减轻细胞凋亡,发挥保护心脏的作用。其机制可能为AS进展中心肌细胞发生氧化应激损伤,NLRP3炎症小体表达增加,激活TGF-β1/Smad3通路诱导心肌细胞外基质重塑修复受损心肌组织,同时TGF-β1的过度分泌也会促进心肌细胞凋亡的发生,而有氧运动能够降低AS小鼠炎症反应阻止上述过程。此外,在心肌梗死动物模型中,研究表明有氧运动并不能降低TGF-β1表达,这可能与不同的动物模型和运动强度有关[49]。

综上所述,有氧运动可以缓解心肌细胞凋亡,减轻心肌损伤,其机制可能与抑制炎症反应、降低心肌酶含量等有关。

作者贡献度说明:

马甜甜负责文章构思;秦芳、于子夫负责数据统计、绘制图表;刘西花对整体研究方案、设计、研究实施过程等进行指导,对论文整体负责。

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