

☆ 综 述 ☆

近10年艾灸治疗膝关节骨关节炎的机制研究进展

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【摘 要】 膝关节骨关节炎(KOA)是中老年人常见的高致残性退行性骨关节病。艾灸已广泛应用于治疗KOA,从多途径发挥效应,疗效显著。本文检索近10年国内外艾灸治疗KOA的相关文献,归纳整理后从抑制炎症反应、促进关节组织修复、调节免疫和肠道菌群方面阐述艾灸起效机制,并在当前研究基础上进行思考与展望,以期今后的相关机制研究提供参考。

【关键词】 艾灸;膝关节骨关节炎;机制;综述

Research progress on the mechanism of moxibustion in the treatment of knee osteoarthritis in the past decade

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【ABSTRACT】 Knee osteoarthritis (KOA) is a common, highly disabling degenerative osteoarthropathy among middle-aged and elderly people. Moxibustion has been widely used in the treatment of KOA and exerts effects through multiple pathways with remarkable curative effects. This paper retrieved the relevant literature on moxibustion in the treatment of KOA at home and abroad in the past 10 years. After sorting and summarizing, it elaborated on the effective mechanisms of moxibustion from aspects such as inhibiting inflammatory responses, promoting the repair of joint tissues, regulating immunity and gut microbiota. Based on the current research, it also carried out thinking and prospects, aiming to provide references for relevant mechanism research in the future.

【KEYWORDS】 Moxibustion; Knee osteoarthritis; Mechanism; Review

膝关节骨关节炎(KOA)以局部疼痛、肿胀和活动障碍等为主要表现,是累及滑膜、软骨和软骨下骨等全关节组织的常见病^[1]。KOA好发于中老年人,致残率高^[1],骨关节炎患者合并高血压、心血管疾病、精神健康等问题的风险也高于正常人^[2]。随着人类平均寿命延长和全球人口老龄化现状不断加剧,该病造成的个人和社会负担日益凸显^[3]。而目前KOA的治疗手段仍有待改善^[4]。非甾体抗炎药是治疗KOA的一线药物,但存在较明显的胃肠道不良反应,透明质酸及生物制剂等关节腔注射的疗效还需更多高质量的临床研究支持^[1]。关节置换术是拯救晚期KOA患者的可行方法,但术后感染和慢性疼痛等并发症仍造成诸多困扰^[4]。因此,探寻安全有效、不良反应小的治疗方式并及时进行干预,是控制KOA病情进展的关键。

艾灸在缓解KOA症状、恢复关节功能、提高生活质量等方面效果显著^[5-7]。近年来艾灸治疗KOA的机制研究已取得一定进展,但缺乏系统总结。本文通过检索2014年1月以来近10年国内外的相关文献,总结出艾灸治疗KOA的机制涉及抑制炎症反应、促进关节组织修复、调节免疫和肠道菌群等。现对相关机制研究进行综述。

1 艾灸抑制KOA炎症反应

1.1 艾灸调节KOA炎症因子

持续存在的炎症反应是KOA病情变化的重要原因。例如肿瘤坏死因子 α (TNF- α)、白细胞介素(IL)-1 β 、IL-6、环氧合酶-2(COX-2)等促炎介质在关节滑膜、软骨组织和外周血中的大量释放,能够直接或间接造成机体炎性疼痛、加速关节病理改

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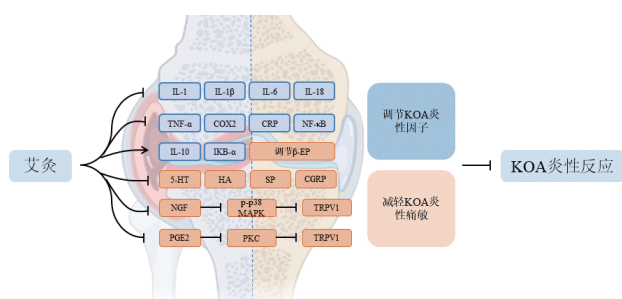
变。多项研究^[8-11]显示艾灸降低 KOA 动物模型血清、关节液和关节软骨组织中 IL-1 β 、TNF- α 含量,抑制血清内 IL-18 表达^[12]、降低 COX-2 水平^[13],提高抗炎因子 IL-10 含量^[14-15],控制局部与全身炎症反应。核转录因子 κ B(NF- κ B)是调控免疫与炎症反应的重要角色,以 p65/p50 异二聚体的形式在机体内广泛分布,NF- κ B 受 IL-1 β 、TNF- α 等炎症因子激活后又能继续刺激促炎因子分泌^[16]。艾灸能有效抑制 KOA 兔关节液内 NF- κ B 表达^[17],下调 KOA 大鼠膝关节软组织中 NF- κ B p65 蛋白表达、上调其抑制物核因子 κ B 抑制蛋白 α 蛋白表达^[18],直接抑制滑膜细胞内致炎物质的合成与分泌^[18]。同时,研究^[7, 19-22]表明艾灸在临床应用中也能有效下调 KOA 患者血清内 C 反应蛋白、IL-1、IL-1 β 、IL-6、TNF- α 等炎症因子表达及 COX-2 含量,抗炎效应显著。热敏灸是在常规艾灸的基础上对敏感腧穴进行探查并施灸的方法,灸热传递更加深入和广泛,相关研究显示其对关节炎的疗效优于常规艾灸^[5, 23]。临床研究^[24-29]亦证实热敏灸能够控制 KOA 患者体内促炎因子水平、增加抗炎因子表达,并逐步改善关节功能。此外,文献报道^[30-34]也表明艾灸联合其他疗法能下调诸多炎症介质表达,缓解症状,提高 KOA 患者生存质量。

1.2 艾灸减轻 KOA 炎性痛敏

KOA 疼痛程度随疾病周期而加重,炎症反应已然成为其中的关键因素。艾灸不仅降低炎症因子水平,还能够下调机体 5-羟色胺、组胺、神经肽、P 物质、降钙素基因相关肽等与诱导痛觉过敏相关的炎症介质表达^[35-36],缓解炎性疼痛,并对关节软骨有一定保护作用。此外,抑制介导炎性疼痛的相关信号通路激活,是艾灸改善 KOA 炎性痛敏的又一机制。背根神经节(DRG)神经元能够敏感传递机体出现的异常感觉,炎症状态使 DRG 神经元内的神经生长因子(NGF)表达增加,激活 p38 丝裂原活化蛋白激酶(p38 MAPK)途径,该途径继续刺激使瞬时感受器电位香草酸受体 1(TRPV1)表达增加,三者共同参与炎性痛敏反应^[37]。研究表明艾灸对 NGF/p38 MAPK/TRPV1 通路发挥抑制作用^[38]。另外,蛋白激酶 C(PKC)参与慢性疼痛,KOA 状态下高表达的炎症因子前列腺素 E2(PGE2)能通过 PKC 促使 TRPV1 磷酸化,激活 PGE2/PKC/TRPV1 信号通路,产生炎性痛敏。研究^[39]显示,热敏灸“犊鼻”可下调 KOA 兔血清 PGE2、DRG PKC 及穴区皮肤 TRPV1 mRNA 表达,抑制 PGE2/PKC/TRPV1 信

号通路激活,减轻炎症反应和局部疼痛。麦粒灸是将艾绒放置于腧穴皮肤及机体反应点直接施灸的艾灸方法,量小效专。研究^[40-41]报道,联合使用麦粒灸和其他疗法的干预方式消炎镇痛作用显著,有效降低了 KOA 患者血清 PGE2 水平,且可调节血清 β -内啡肽(β -EP)水平。 β -EP 具有强效镇痛作用,然而艾灸治疗后 KOA 患者体内 β -EP 水平的变化趋势仍需进一步探索,其是否与 KOA 病情进程、艾灸治疗时间及疗程等因素相关值得深入挖掘。

上述研究显示,艾灸通过抑制促炎因子释放、增加抗炎因子表达以调整机体炎症状态,并调节诱导炎性疼痛的炎症介质与信号通路,控制炎症反应级联反应,发挥抗炎镇痛作用。见图 1。



注:→表示促进作用;—|表示抑制作用,下图同。KOA 为膝关节骨关节炎,IL 为白细胞素,TNF- α 为肿瘤坏死因子- α ,COX-2 为环氧酶-2,CRP 为 C 反应蛋白,NF- κ B 为核转录因子 κ B,I κ B- α 为核因子 κ B 抑制蛋白 α , β -EP 为 β -内啡肽,5-HT 为 5-羟色胺,HA 为组胺,SP 为 P 物质,CGRP 为降钙素基因相关肽,NGF 为神经生长因子,p38 MAPK 为 p38 丝裂原活化蛋白激酶,TRPV1 瞬时感受器电位香草酸受体 1,PGE2 为前列腺素 E2,PKC 为蛋白激酶 C。

图 1 艾灸抑制 KOA 炎性反应示意图

Fig. 1 Schematic diagram of moxibustion inhibiting KOA inflammatory response

2 艾灸促进 KOA 关节组织修复

2.1 艾灸调控 KOA 软骨代谢

关节软骨无血管、神经分布,主要由软骨细胞和细胞外基质(ECM)组成,其中 II 型胶原和蛋白多糖是形成 ECM 的必要成分^[42]。KOA 炎症反应刺激会造成软骨细胞异常凋亡,ECM 过度降解,破坏软骨代谢。

2.1.1 调节基质金属蛋白酶(MMPs)

MMPs 与 KOA 关系密切,其中 MMP-1、MMP-3、MMP-9、MMP-13 等多个成员在降解 ECM、参与软骨破坏方面占据重要地位^[43]。研究显示,艾灸能够降低 KOA 动物模型血清与滑膜组织内 MMP-13 表

达^[44],下调MMP-3、MMP-9表达^[45],保护软骨组织。血管内皮生长因子(VEGF)具有抑制ECM合成和促进多种MMPs分泌的功能^[46]。基质金属蛋白酶抑制剂(TIMPs)在关节炎状态下能抑制MMPs活性,维持二者比例平衡是缓解KOA软骨退变的机制之一^[47]。研究^[47]表明,艾灸能下调KOA兔软骨组织、滑膜及关节滑液内VEGF、MMP-9表达,纠正MMP-9/TIMP-1比例失衡,减轻关节炎性反应并延缓软骨退行性病变。艾灸对MMPs的下调作用在诸多临床研究中也得到证实。相关研究报道,热敏灸膝关节局部腧穴^[6, 48]及重灸阴陵泉、阳陵泉^[49]能够有效降低KOA患者血清MMP-3含量,艾灸联合其他疗法干预可明显下调KOA患者血清MMP-1^[50-51]、MMP-13^[52]表达,麦粒灸联合康复训练干预能够抑制KOA患者血清MMP-9、TIMP-1及组织蛋白酶D水平^[51],提示艾灸在降低关节软骨损伤风险方面具有重要价值。

2.1.2 调节软骨细胞凋亡和ECM降解

凋亡是导致KOA关节软骨退变的重要病理环节,天冬氨酸特异性半胱氨酸蛋白酶-3(Caspase-3)和抑癌基因p53编码蛋白(p53)在诱导细胞凋亡方面具有独特作用。由于KOA关节局部炎症因子分泌旺盛,解聚蛋白样金属蛋白酶(ADAMTS)-4水平和诱导型一氧化氮合成酶(iNOS)含量因此大幅升高,iNOS进一步增加一氧化氮(NO)生成,损害软骨细胞与ECM。研究显示,热敏灸“犊鼻”能够降低KOA兔软骨组织内p53、Caspase-3表达^[53-54],阻止关节软骨细胞过度凋亡,并抑制血清内NO和关节软骨内ADAMTS-4表达^[55],降低关节软骨iNOS含量^[56],升高ECM组成物Ⅱ型胶原^[56]和蛋白多糖^[55]表达,保护软骨基质,促进软骨修复。艾烟是艾灸疗效的一部分,包含诸多化学成分,能调控机体免疫,发挥抗炎抑菌等多种药理特性^[57]。研究^[58]证实艾烟浓度与修复KOA软骨组织密切相关,较高浓度的艾烟环境能上调具备抗凋亡作用的Bcl-2蛋白含量、下调凋亡蛋白启动子BAX含量,这被认为可能是艾灸疗法调节软骨代谢的机制之一。热敏灸能增加KOA患者血清内胰岛素样生长因子-1(IGF-1)、成纤维细胞生长因子-2(FGF-2)及转化生长因子- β 1(TGF- β 1)含量^[27],调节软骨细胞生长,促进关节软骨修复。此外,隔药艾灸显著降低了KOA患者血清内硫酸软骨素846(CS846)、钙卫蛋白S100A8/A9水平^[59],阻止软骨细胞分解代谢物过度释放。

2.1.3 调节氧化应激(OS)

OS与KOA的关系已经得到证实^[60],生理状态下,活性氧(ROS)参与机体软骨代谢,调节软骨细胞的生长凋亡和ECM的合成降解,但KOA炎性刺激使ROS物质在体内滞留,诱发OS反应^[61]。OS生物标志物丙二醛(MDA)表达随之增高,而超氧化物歧化酶(SOD)活力降低,提示机体清除滞留氧自由基的能力下降,该反应会放大KOA病理因素对关节软骨细胞和ECM的负面作用。研究^[7, 62]显示艾灸能降低KOA患者血清内MDA、关节液内NO含量,增加SOD活力,恢复机体氧自由基生成与消除的动态平衡,改变软骨基质降解恶性加快的局面,有效保护软骨组织。

2.2 艾灸调控KOA骨代谢

抗酒石酸盐酸性磷酸酶(TRACP)与Ⅰ型胶原蛋白C末端异肽(CTX-I)是观察骨质代谢的客观指标。研究^[6, 48, 63-64]显示,热敏灸能够下调KOA患者血清内CTX-I、TRACP、TRACP-5b、ADAMTS-4、MMP-3表达,抑制破骨细胞活化,调节骨代谢,延缓关节退变。雌激素水平下降是绝经后女性罹患骨关节炎的危险因素之一^[65],维持雌激素正常水平有助于保持关节稳态,并抑制炎症因子对骨及软骨的破坏作用^[66],研究^[67]显示艾灸联合关节腔内玻璃酸钠注射能够明显升高绝经后KOA女性患者外周血中雌二醇含量,抑制过度骨吸收。

2.3 艾灸调节KOA关节修复相关信号通路

2.3.1 c-Jun氨基末端激酶(JNK)信号通路

已知KOA疾病进程涉及多条信号通路^[68],其中JNK信号通路参与软骨损害,其基因编码产物JNK1、JNK2在机体分布广泛,炎症因子能诱导JNK磷酸化,从而激活JNK信号通路,促使MMPs表达持续增加。温和灸能抑制KOA兔体内JNK1、JNK2蛋白表达,阻止JNK信号通路激活,继而降低MMP-1、MMP-13含量^[69],调节软骨基质合成与降解。

2.3.2 p38 MAPK相关信号通路

机体炎症反应与应激反应均可激活p38 MAPK信号通路,该信号通路不仅参与炎症痛敏^[38],还与关节软骨内稳态紧密相关,能调控软骨细胞生长凋亡和MMPs炎性介质分泌。研究^[12]显示艾灸显著下调KOA大鼠软骨组织内磷酸化(p)-p38、MMP-13蛋白表达,抑制p38 MAPK信号通路。小窝蛋白1(Caveolin-1)是p38 MAPK信号通路上游的重要信号分子,其高表达能够诱导该通路激活,进而参与破坏软骨细胞和ECM合成。研究^[70]显示,艾灸下调

KOA 兔软骨组织中 Caveolin-1 蛋白表达、降低 p38 MAPK 蛋白活性,抑制 Caveolin-1/p38 MAPK 通路异常激活,减少炎症因子释放,延缓关节软骨进行性退变。

2.3.3 Wnt/ β -连环蛋白(β -catenin)信号通路

Wnt/ β -catenin 信号通路与炎症反应、骨稳态有重要联系,生理状态下能够调控骨、软骨及关节的生长发育^[71],而炎症刺激使 Wnt 信号被激活后继续活化下游因子 β -catenin,二者促进 MMPs、ADAMTS-5、骨形成蛋白-2(BMP-2)、COX-2 等分泌,加速 KOA 软骨退变^[68]。研究^[8, 72]显示艾灸能够抑制 KOA 动物模型 Wnt/ β -catenin 信号通路活化,下调膝关节软骨组织中关键因子 Wnt-3 α 、 β -catenin、BMP-2 表达,抑制 MMP-3、MMP-9、MMP-13 mRNA 及蛋白表达,控制软骨基质降解,延缓软骨退变。

2.3.4 NF- κ B 信号通路

NF- κ B 活跃于机体炎症反应及免疫应答中。KOA 病理状态下,IL-1 β 、TNF- α 等经典促炎因子能够激活 NF- κ B 信号通路,该信号通路继而诱导产生 COX-2、PGE2、MMPs 等多种促炎和促软骨分解代谢因子^[16],因此 NF- κ B 信号通路在 KOA 炎症进展与软骨退变中具有关键地位。研究^[73]表明,热敏灸“犊鼻”能抑制 NF- κ B 信号通路激活,下调 KOA 兔关节软骨内 NF- κ B p50、NF- κ B p65 表达,降低血清

和关节液内 IL-1 β 含量,减轻对软骨基质的损害,并升高关节软骨内 II 型胶原表达,促进软骨组织修复。

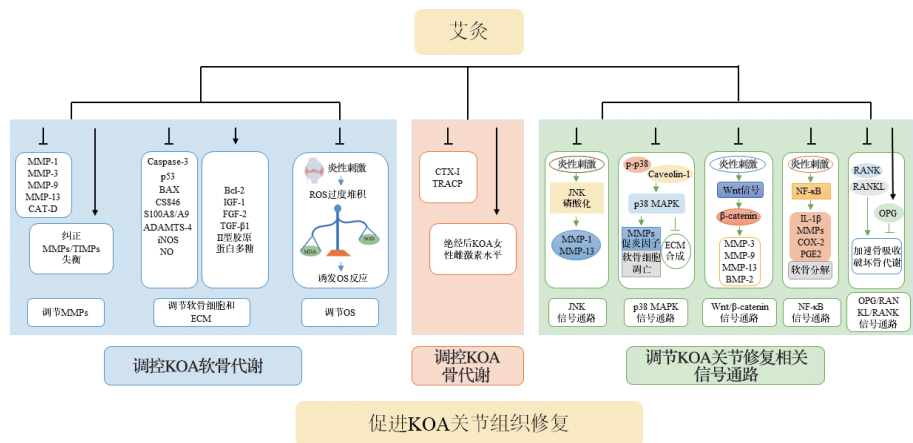
2.3.5 OPG/RANKL/RANK 信号通路

研究指出,核因子 κ B 受体活化因子(RANK)及 RANK 配体(RANKL)的结合加速破骨细胞分化,促进骨吸收以破坏骨代谢平衡,而骨保护素(OPG)的释放能抑制过度骨吸收^[74]。因此 OPG/RANKL/RANK 信号通路在调节骨代谢、平衡成骨和破骨细胞功能方面具有重要作用。研究^[45]表明,艾灸通过调控 KOA 兔体内 OPG/RANKL/RANK 信号通路,升高 OPG 蛋白水平,降低 RANK、RANKL 蛋白水平,并抑制 MMP-3、MMP-9、IL-1 的表达,阻止软骨下骨的进行性损坏与降解。

以上研究提示,艾灸通过调节多条信号通路、抑制软骨和骨代谢紊乱,最终促进关节组织修复与结构重建。见图 2。

3 艾灸调节 KOA 机体免疫

研究表明免疫细胞浸润在 KOA 炎症反应中十分常见^[75-76],免疫细胞是影响 KOA 病情变化的重要调节器。其中,T 淋巴细胞及其亚群辅助性 T 细胞(Th)与 KOA 滑膜炎性反应、软骨和软骨下骨损伤、机体免疫环境稳定密切相关。Th17 能够释放 IL-17、IL-21 等促炎因子,Th22 可增加炎症因子 IL-13、



注:KOA为膝关节骨关节炎,ECM为细胞外基质,MMP为基质金属蛋白酶,CAT-D为组织蛋白酶D,TIMPs为基质金属蛋白酶抑制剂,Caspase-3为天冬氨酸特异性半胱氨酸蛋白酶-3,p53为p53编码蛋白,CS846硫酸软骨素846,ADAMTS-4为解聚蛋白样金属蛋白酶-4,iNOS为诱导型一氧化氮合成酶,NO为一氧化氮,IGF-1为胰岛素样生长因子-1,FGF-2为成纤维细胞生长因子-2,TGF- β 1为转化生长因子- β 1,ROS为活性氧,OS为氧化应激,CTX-I为I型胶原蛋白C末端异物肽,TRACP为抗酒石酸盐酸性磷酸酶,Caveolin-1为小窝蛋白1,p38 MAPK为p38丝裂原活化蛋白激酶, β -catenin为 β -连环蛋白,BMP-2为骨形成蛋白-2,NF- κ B为核转录因子 κ B,IL-1 β 为白细胞介素1 β ,COX-2为环氧化酶-2,PGE2为前列腺素E2,RANK为核因子 κ B受体活化因子,RANKL为核因子 κ B受体活化因子配体,OPG为骨保护素。

图 2 艾灸促进 KOA 关节组织修复示意图

Fig. 2 Schematic diagram of moxibustion promoting KOA joint tissue repair

IL-22、TNF- α 等表达^[77]。研究显示,艾灸联合经筋推拿运用能够调节KOA患者体内T淋巴细胞水平^[30],下调Th17、Th22表达^[78],阻止炎症反应持续加重,减轻免疫损伤。巨噬细胞是参与固有免疫的关键因子,在不同因素刺激下可极化为不同亚群,调控机体炎症状态。其中,M1型巨噬细胞能够诱导IL-1 β 、TNF- α 等多种促炎因子分泌并参与骨破坏,而M2型增加IL-10、TGF- β 等抗炎因子释放,促使炎症反应消退与组织修复^[79-80]。艾灸“足三里”能上调KOA大鼠膝关节滑膜组织巨噬细胞标志物CD206表达,促使巨噬细胞向具有抗炎特性的M2型极化,增加抗炎因子IL-10表达,调节固有免疫,减轻关节炎症反应^[79]。

4 艾灸调节KOA机体肠道菌群

肠道菌群由庞大的微生物群体组成,微生物种群间相互依赖并维持动态平衡,使机体具有应对外界环境变化的免疫力。研究^[81-82]显示肠道菌群与多种疾病存在联系。肠道菌群失调加重骨关节炎病变的可能机制包括3个方面^[83-84]:其一是打破肠道屏障,给予肠内细菌和促炎物质脂多糖等进入体循环的通道;其二在于肠道菌群代谢紊乱,诱导促炎介质异常释放;其三是肠道菌群失调导致微量元素水平波动,破坏关节内环境,加剧炎症反应与软骨损害。肠道菌群可能通过调节免疫、内分泌等影响KOA病情发展^[85],肠-关节轴已成为治疗KOA的新靶点。研究^[9-10, 14]显示与艾灸组大鼠相比,KOA模型组大鼠体内存在明显的肠道菌群紊乱,而艾灸干预能显著改善KOA大鼠肠道菌群失调,逐步恢复肠道菌群多样性,增加益生菌丰度、减少致病菌,下调炎症因子表达,增强其抗炎能力。

5 小结

目前艾灸治疗KOA的机制已围绕抑制炎症反应、促进关节组织修复、调节免疫和肠道菌群等多方面展开,其中调控炎症反应与保护关节软骨仍是机制研究的热点。结合现有机制研究的文献报道,笔者认为在未来研究中有以下值得注意之处:(1)由于KOA常见于中老年群体,故实验动物年龄段的选择应注意与疾病的适配度;不同的KOA模型制备方法存在研究侧重点,在实验设计中值得进一步考量,如Hulth、前交叉韧带和半月板切除等手术造模更偏向于研究创伤型KOA,关节腔注射碘乙酸、木瓜蛋白酶等则更适用于观察软骨病理改变与炎症反应^[86];(2)艾灸能显著改善寒湿痹阻^[5, 87]、肝肾

亏虚^[21, 27]及阳虚寒凝^[6, 25]等KOA患者病情,而目前实验研究中缺乏病证结合的KOA模型;(3)当前艾灸治疗KOA的机制研究多以局部腧穴为操作部位,对辨证选穴与腧穴配伍关注不足;(4)艾灸促进KOA炎症反应消退已取得一定进展,但在趋化因子、TLRs、Notch等致炎信号通路及中枢机制等方面仍有探索空间;(5)各类机制在KOA病程中往往相互交织,而目前相关研究的关注点较为单一,未来可加强探索不同机制间的联系;(6)量效、时效是艾灸治疗的重要因素,影响着KOA的观察指标与最终疗效^[15, 44, 48, 88],但目前研究量较少,仍有待挖掘。

综上,未来研究应在当前基础上更加深入探讨KOA致病环节和艾灸起效途径,多方位、深层次揭示艾灸治疗KOA的相关机制,发掘更多治疗靶点,为临床应用提供指导。

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