

基于PI3K/Akt信号通路探讨糖尿病创面愈合的中药干预策略

叶杜, 俞赞丰, 苏思雅, 王颖, 褚书舟, 朱俊平, 喻嵘^{*}
(湖南中医药大学 中医学院, 长沙 410208)

[摘要] 糖尿病创面(DW)是糖尿病严重并发症之一,因其迁延难愈和高复发率成为临床治疗难点。磷脂酰肌醇-3激酶/蛋白激酶B(PI3K/Akt)信号通路在调控细胞增殖、代谢、凋亡和自噬中发挥核心作用,其功能抑制与DW愈合障碍密切相关。现代研究表明,该通路功能障碍可导致炎症因子过度表达、氧化应激加剧、细胞凋亡增加及自噬紊乱,从而延缓创面修复。中医药以整体观和辨证论治为指导,具有多成分、多靶点、整体调节的优势。诸多中药单体及复方可通过调控PI3K/Akt信号通路,抑制核转录因子- κ B(NF- κ B)等炎症信号转导,增强抗氧化酶活性,调节凋亡与自噬平衡,并促进血管内皮生长因子等表达,从而改善高糖微环境下细胞功能,协同促进创面愈合。该文立足于“正气亏虚、瘀毒阻络”的中医病机,提出“扶正解毒、化瘀通络”为中医干预DW的核心治法,总结中药可通过益气活血、温阳通脉、清热解毒等不同治法多维度调控PI3K/Akt信号通路,体现中医药“病证结合、标本兼治”的独特优势。未来研究应结合系统药理学与临床验证,深入阐释中药多成分协同调控PI3K/Akt网络的作用机制,为中医药防治DW提供更充分的科学依据。

[关键词] 糖尿病创面; 磷脂酰肌醇-3-激酶/蛋白激酶B(PI3K/Akt)信号通路; 中医药干预; 多靶点治疗

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Traditional Chinese Medicine Intervention Strategies for Diabetic Wound Healing Based on PI3K/Akt Signaling Pathway

YE Du, YU Yunfeng, SU Siya, WANG Ying, CHU Shuzhou, ZHU Junping, YU Rong^{*}
(School of Chinese Medicine, Hunan University of Chinese Medicine, Changsha 410208, China)

[Abstract] Diabetic wound (DW) is one of the serious complications of diabetes and has become a clinical challenge due to its protracted, refractory nature and high recurrence rate. The phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) signaling pathway plays a core role in regulating cell proliferation, metabolism, apoptosis, and autophagy, and its functional inhibition is closely associated with impaired DW healing. Modern studies have demonstrated that dysfunction of this pathway can lead to overexpression of inflammatory factors, aggravated oxidative stress, increased apoptosis, and dysregulated autophagy, thereby delaying wound repair. Guided by the holistic concept and treatment based on pattern identification, traditional Chinese medicine (TCM) possesses the advantages of multi-component, multi-target, and holistic regulation. Numerous TCM monomers and compound formulas can regulate the PI3K/Akt signaling pathway, inhibit inflammatory signal transduction mediated by nuclear factor- κ B (NF- κ B) and others, enhance antioxidant enzyme activities, modulate the balance between apoptosis and autophagy, and promote the expression of vascular endothelial growth factor (VEGF) and other factors, thereby improving cellular functions in a high-glucose microenvironment and synergistically facilitating wound healing. Based on the TCM pathogenesis of "deficiency of vital Qi, stasis and toxin obstructing collaterals", this paper proposes "reinforcing vital Qi and removing toxin, resolving stasis and dredging collaterals" as the core therapeutic principle for TCM intervention in DW, and summarizes that Chinese medicinals can multi-dimensionally regulate the PI3K/Akt signaling pathway through different treatment methods such as supplementing Qi and

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[第一作者] 叶杜,在读硕士,从事经方理论与应用研究,E-mail:1939463954@qq.com

[通信作者] ^{*}喻嵘,博士,博士生导师,教授,从事经方理论与应用研究,E-mail:yuron@21.cn.com

activating blood, warming Yang and dredging vessels, and clearing heat and removing toxin, embodying the unique advantage of TCM in "differentiation of disease and pattern, treatment of both the root cause and the manifestations". Future research should integrate systems pharmacology with clinical validation to deeply elucidate the mechanisms of multi-component synergistic regulation of the PI3K/Akt network by Chinese medicinals, providing more sufficient scientific evidence for the prevention and treatment of DW with TCM.

[Keywords] diabetic wounds; phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) signaling pathway; traditional Chinese medicine intervention; multi-target therapy

糖尿病创面(DW)是指在慢性高血糖状态下发生的皮肤组织损伤或溃疡,属于糖尿病常见且严重的并发症之一。全球范围内,DW每年影响约1 860万人,其发病率近年来持续上升^[1-2]。我国50岁以上糖尿病患者中DW的发病率高达8.1%,愈合后患者1年内再发溃疡的比例为31.6%^[3],反映出该病具有高复发性和难愈性的特点。临床表现多以糖尿病周围神经病变及组织损毁为主^[4],易合并感染^[5],严重者甚至需截肢^[6],给患者带来沉重的经济和心理负担^[7]。临床采用多种防治策略,但因DW发病机制复杂,牵涉诸多病理学过程^[8],使其成为临床治疗的难点。从中医学角度看,其发病与“虚、毒、瘀”密切相关,消渴日久,正气亏虚为本,机体失于濡养;血行不畅,瘀阻络脉,局部气血壅滞;加之燥热内蕴,或外邪侵袭,化生浊毒,蚀肉损筋,三者交织为患,导致创面经久不敛。其核心病机可概括为“虚、瘀、毒”三者交织。其中,“虚”是正气亏虚,乃发病之本,表现为组织再生与修复动力不足;“瘀”是血行瘀滞,为核心病理环节,导致局部微循环障碍;“毒”是湿热浊邪蕴结,为致病之标,加剧组织损伤与炎症反应。三者互为因果,共同导致创面难愈。中药有效成分及其复方,基于“扶正补虚、化瘀解毒”的治法,因其多靶点、低毒性、疗效显著等优势,在DW治疗中展现出巨大的潜力。磷脂酰肌醇3-激酶/蛋白激酶B(PI3K/Akt)是体内经典的信号通路,不仅参与葡萄糖代谢,更是与DW的发生发展密切相关^[2,9]。近年研究表明,该通路可作为促进DW愈合的关键靶点。以下基于PI3K/Akt信号通路在DW中的作用机制,并结合中药有效成分及复方通过调控该通路促进创面修复的研究,以期中医药靶向治疗DW提供理论依据,推动其在基础研究与临床转化中的应用。

1 从“虚、毒、瘀”论DW病因病机

DW在中医学中可归属于“脱疽”“痈疽”“浸淫疮”等范畴。其病因病机核心与“虚、毒、瘀”三者密切相关。消渴病日久,气阴两虚为其本,阴虚内热,耗伤津血,津亏不能载血,气虚无力行血,致血液凝滞,形成血瘀;瘀血阻滞络脉,气血津液输布受阻,肢体末端失于濡养,则见皮肤干燥、感觉异常。在此基础上,稍受外邪侵袭或局部损伤,即可因正虚不能托毒外出,瘀久化热,热盛肉腐,化生痈疽,瘀热积盛则酿化为毒,毒邪炽盛,进一步损伤经络,腐筋蚀骨,故见创面溃烂、脓液潴留、久不收敛、甚则变黑坏死。虚、瘀、毒三者相互胶结,虚愈甚则瘀愈重,毒愈炽;毒愈盛则气阴愈伤,血络愈阻,从而形成虚实夹杂、恶性循环的病理局面,致使创面缠绵难愈,甚则内陷攻心,变证丛生。王永炎院士强调“虚气留滞”是慢性疾病的核心病机,正气亏虚为其重要始动环

节^[10]。国医大师张学文认为糖毒、浊毒、热毒、瘀毒是糖尿病足常见的致病因素^[11]。综上,DW的发生与发展,深刻体现了虚、瘀、毒交织作用的病机演变过程。

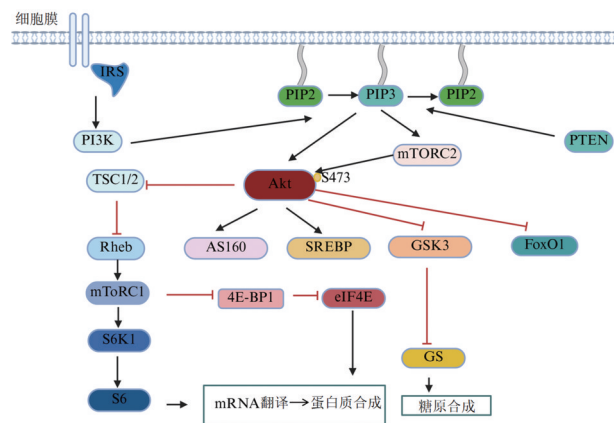
2 PI3K/Akt信号通路概述

PI3K/Akt信号通路是调控细胞增殖和代谢的关键通路。其激活依赖于胰岛素、生长因子等刺激^[9]。根据序列同源性和脂质底物偏好的差异,PI3K分为I类、II类和III类,其中I类PI3K研究最广泛。I类PI3K通过磷酸化Akt(Thr308/Ser473位点)传递下游信号,参与糖代谢调控,关键分子包括胰岛素受体底物(IRS)、PTEN蛋白(PTEN)、雷帕霉素靶蛋白复合物1/2(mTORC1/2)等^[12]。Akt是一种丝氨酸/苏氨酸激酶,是多种细胞活动的重要信号中枢功能。PI3K依赖的Akt激活进一步影响参与细胞增殖、血管生成、衰老的几个下游通路的活性^[13-14]。PI3K/Akt信号通路在正常组织修复过程中至关重要,在受损组织的再生^[15]、重塑^[16]和重新上皮化^[17]中发挥着关键作用。失调的PI3K/Akt信号通路对伤口愈合有显著影响^[18]。PI3K/Akt信号通路活性显著降低,导致成纤维细胞增殖迁移受阻及胶原沉积异常。研究表明,脂肪源性干细胞通过释放外泌体促进成纤维细胞增殖和迁移,并通过PI3K/Akt信号优化胶原蛋白沉积来促进伤口愈合^[19]。值得注意的是,与DW相关的PI3K、Akt的活性,在DW中显著降低^[13]。因此,恢复PI3K/Akt信号通路活性是改善DW愈合的关键策略。PI3K/Akt信号通路概述见图1。

3 PI3K/Akt信号通路调控DW的作用机制

DW愈合障碍涉及多种病理生理改变的共同作用,包括持续的组织缺损、创面感染、高截肢风险及死亡率增加等^[13]。PI3K/Akt信号通路作为一条重要的细胞内信号转导途径,其活性下降与胰岛素敏感性降低及糖尿病发生发展密切相关^[14]。在高糖环境下,该通路的活性受到显著抑制,进而影响下游多种生物学过程,最终导致创面修复障碍。以下将从炎症与氧化应激、细胞增殖与凋亡、细胞自噬3个方面,系统阐述PI3K/Akt信号通路在DW愈合中的调控机制。

3.1 炎症与氧化应激 DW愈合障碍主要表现之一为炎症反应过度与氧化应激损伤,共同导致创面修复延迟。在正常愈合过程中,炎症期是清除病原体及坏死组织的关键阶段,体内白细胞表型及数量恢复原状通常于1~2周内逐步消退^[20]。然而,在高糖微环境中,晚期糖基化终末产物(AGEs)积累并通过受体加剧损伤;激活核转录因子- κ B(NF- κ B)信号通路,引起白细胞介素(IL)-1 β 、IL-6、肿瘤坏死因子- α (TNF- α)等促炎因子过度表达,形成持续性炎症状态^[21-22]。同时,高糖诱导多元醇通路、蛋白激酶C等代谢途径异常激



注: SREBP. 固醇调节元件结合蛋白; AS160. Akt底物 160kDa; TSC1/2. 结节性硬化症复合物 1/2; FoxO1. 叉头框蛋白 O1; GSK3. 糖原合成酶激酶 3; Rheb. 脑富集 Ras 同源蛋白; PIP2. 磷脂酰肌醇二磷酸; PIP3. 磷脂酰肌醇三磷酸; 4E-BP1. 真核翻译起始因子 4E 结合蛋白 1; Eif4E. 真核起始因子 4E; S6K1. 丝氨酸/苏氨酸蛋白激酶; S6. 核糖体蛋白; GS. 糖原合酶

图1 PI3K/Akt信号通路概述

Fig. 1 Overview of PI3K/Akt signaling pathway

活,导致活性氧(ROS)大量产生^[23],而机体抗氧化能力因糖代谢紊乱而下降^[24],抗氧化酶如超氧化物歧化酶(SOD)和谷胱甘肽过氧化物酶(GSH-Px)活性降低^[23,25],进一步加剧氧化应激^[26]。中性粒细胞过度浸润并释放 ROS 及促炎因子,损伤细胞膜与细胞外基质(ECM)。同时,基质金属蛋白酶(MMP)表达上调而其 MMP 抑制剂生成不足,平衡破坏,引起 ECM 过度降解,阻碍成纤维细胞介导的组织修复,导致创面停滞于炎症期^[27-29]。PI3K/Akt 信号通路在调控炎症与氧化应激中发挥核心作用。在非糖尿病和糖尿病大鼠的组织中,Akt 信号通路受到刺激,该通路相关的总蛋白和磷酸化蛋白显著增加^[30]。HOKE 等^[13]发现,在 DW 中,与 PI3K/Akt、NF- κ B 和 β -连环蛋白通路相关的 PI3K、Akt、GSK3 β 、哺乳动物雷帕霉素靶蛋白(mTOR)、磷酸化(p)-mTOR、NF- κ B 和胱天蛋白酶(Caspase)-3 的表达显著增加。然而,与非 DW 相比,这些蛋白在 DW 中显著减少。在糖尿病中,由于 2-脱氧葡萄糖摄取减少及葡萄糖转运蛋白 1 转运体的表达和调节降低,PI3K/Akt 通路受损,导致葡萄糖代谢减少^[31]。该通路在糖尿病状态下常被抑制,丧失对核因子 E₂ 相关因子 2 (Nrf2)/NF- κ B 等重要信号级联的调控能力,加剧炎症与氧化损伤^[32-33]。激活 PI3K/Akt 可抑制 NF- κ B 活化,下调 IL-6、TNF- α 等促炎因子表达,并促进抗炎介质如 IL-10 和转化生长因子- β (TGF- β)释放,从而缓解过度炎症^[34-35]。在氧化应激方面,该通路的激活可上调 SOD、GSH-Px 等关键抗氧化酶的表达,增强 ROS 清除能力,减轻氧化损伤^[36-39]。此外,PI3K/Akt 信号通路也参与促进成纤维细胞增殖与迁移,推动创面由炎症期向增殖期过渡^[40]。

3.2 细胞增殖和凋亡 在 DW 愈合过程中,PI3K/Akt 信号通路的异常与 microRNA(miRNA)的调控密切相关。多项研究表明,某些 miRNA(如 miR-126 和 miR-21 等)在糖尿病

状态下表达异常,通过靶向作用于 PI3K/Akt 信号通路中的关键信号分子,从而调控该通路的活性。在正常生理条件下,此类 miRNA 表达水平较低,PI3K/Akt 信号得以有效激活,促进细胞增殖、迁移并抑制凋亡;而在高糖环境中,相关 miRNA 水平上升,抑制 PI3K/Akt 信号通路的活性,导致细胞增殖与迁移能力下降,凋亡加剧^[41-42]。细胞凋亡的异常调控是 DW 难以愈合的重要因素之一。该类创面通常表现为肉芽组织形成不良和凋亡细胞比例升高,部分归因于生存信号如生长因子的缺乏及高糖微环境的持续损害^[43]。高糖诱导的氧化应激导致 ROS 大量积累,进而激活 Caspase 信号级联,上调促凋亡蛋白如 Fas 配体(CD95L/FASL)和 B 细胞淋巴瘤-2(Bcl-2)相关 X 蛋白(Bax)的表达,并抑制抗凋亡蛋白 Bcl-2,最终引起细胞凋亡增加^[43-44]。JIANG 等^[45]报道,在慢性创面中伴随胶原结构破坏和生长因子受体表达下调,细胞凋亡显著增强。FRYKBERG 等^[46]进一步指出,氧化应激可诱导 DNA 损伤、细胞衰老及周期停滞,从而促进凋亡发生,这些变化与糖尿病代谢紊乱及细胞内信号网络失调密切相关。此外,PI3K/Akt 信号通路也参与调控血管生成,后者是肉芽组织形成和创面修复的基础。该通路可通过激活内皮型一氧化氮合酶(eNOS)促进一氧化氮生成,并上调血管内皮生长因子(VEGF)、血小板衍生生长因子(PDGF)和碱性成纤维细胞生长因子(bFGF)等关键血管生成因子的表达,从而促进血管新生和组织灌注^[47-49]。在 DW 中,PI3K/Akt 信号受损不仅影响细胞存活与增殖,也导致血管生成障碍,进一步延缓愈合进程。

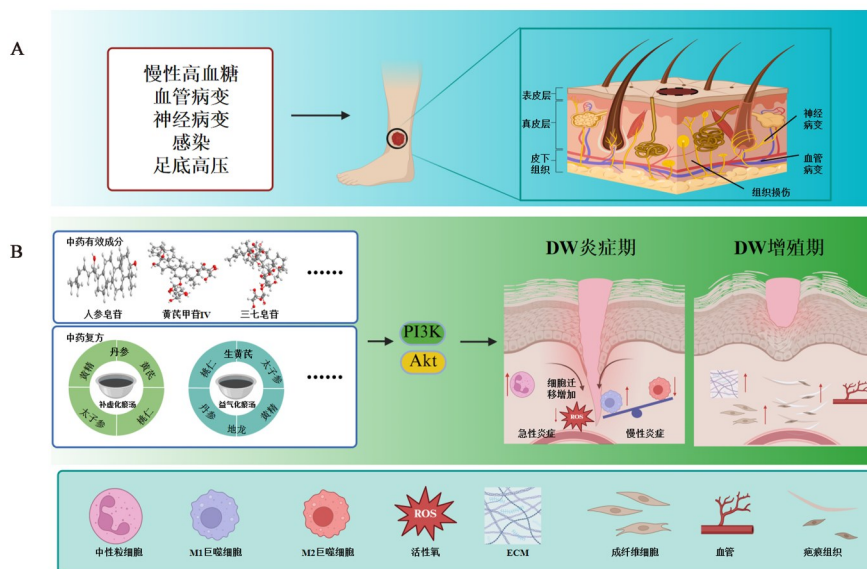
3.3 细胞自噬 自噬是细胞内一种高度保守的分解代谢过程,通过降解受损细胞器、异常蛋白质和病原体,在维持细胞稳态、能量平衡及免疫调节中发挥关键作用^[50-52]。在糖尿病背景下,自噬功能紊乱已成为导致创面难愈的重要机制之一。生理状态下,自噬有助于维持胰岛 β 细胞功能,促进胰岛素分泌并抑制凋亡,从而参与血糖稳态的调节^[53-54];然而,在 DW 中,过度或持续的自噬活化反而加剧细胞损伤和组织修复障碍。高迁移率族蛋白 1 在 DW 中表达升高,可通过抑制 Akt/mTOR 信号通路增强自噬水平,进而引起细胞凋亡增加和组织修复延迟^[55-56]。自噬活性常用标志物如自噬关键分子酵母 Atg6 同系物(Beclin1)和微管相关蛋白 1 轻链 3 II(LC3 II)进行评价,两者也是自噬体形成的关键蛋白^[51-57]。PI3K/Akt/mTOR 信号通路是自噬上游的主要负调控通路。活化的 PI3K 可磷酸化 Akt,进而激活 mTOR,后者通过抑制自噬起始复合物的组装从而抑制自噬^[58-59]。在糖尿病环境中,该通路常受到抑制,导致 mTOR 活性下降,自噬过度激活,最终阻碍创面愈合。研究表明,靶向激活 PI3K/Akt 信号通路可有效抑制异常自噬,改善细胞存活与组织修复。例如,鸢尾素也依赖该通路抑制自噬,缓解胰岛素抵抗并促进愈合过程^[60]。因此,恢复 PI3K/Akt/mTOR 信号通路活性以调控自噬,可能是 DW 治疗的一个有前景的策略。

4 基于 PI3K/Akt 信号通路促进 DW 愈合的中药干预策略

基于上述 PI3K/Akt 信号通路在 DW 愈合关键调控作用的

机制阐述,近年来中医药在该领域的干预潜力日益受到关注。中医药以整体观和辨证论治为指导,具有多成分、多靶点、整体调节的特点,在调控PI3K/Akt信号通路促进DW修复方面展现出显著优势。诸多中药有效成分及复方可通过作用于该通路

上下游关键靶点,有效改善高糖微环境下的细胞功能障碍,协同促进创面愈合进程。结合中药有效成分及复方通过调控PI3K/Akt信号通路促进DW愈合的中药干预策略,为进一步阐明其作用机制及推动临床转化提供参考。见图2。



注:A.DW发生发展的始动因素,包括慢性高血糖、血管病变、神经病变、感染和足底高压等;B.中药或复方通过调控PI3K/Akt信号通路,影响中性粒细胞、巨噬细胞极化、活性氧、细胞外基质、成纤维细胞、血管生成及疤痕组织形成,从而促进糖尿病足愈合

图2 中药经PI3K/Akt信号通路干预DW

Fig. 2 Traditional Chinese medicine intervenes in DW via PI3K/Akt signaling pathway

4.1 中药有效成分调控PI3K/Akt信号通路治疗DW 中药有效成分在调控PI3K/Akt信号通路、促进糖尿病创面愈合方面展现出多靶点、整体调节的作用特点。根据其作用机制的不同,可分为以下几类进行系统性论述,中药有效成分调控PI3K/Akt信号通路治疗DW,见增强出版附加材料^[25,61-67]。

①抑制炎症反应、减轻氧化应激类成分。该类成分主要通过激活PI3K/Akt信号通路,进而抑制NF- κ B等炎症信号转导,并增强抗氧化能力,从而改善DW高炎性、高氧化应激的病理微环境。栀子苷有显著的降血糖作用^[68],可显著促进PI3K和Akt蛋白磷酸化^[69],下调创面组织中TNF- α 、IL-1 β 和IL-6等促炎因子水平,有效抑制局部过度炎症与细胞凋亡,促进创面愈合^[61]。山竹子素则通过抑制PI3K/Akt/NF- κ B信号通路,下调巨噬细胞分泌的炎症细胞因子,同时改善血管生成并抑制细胞焦亡,协同促进创面修复^[63]。黄芪甲苷IV具有抗炎、抗氧化应激的作用^[70],不仅能通过PI3K/Akt/mTOR信号通路促进血管生成相关因子表达,研究还提示其可能通过调节PI3K/Akt/Nrf2轴增强SOD等抗氧化酶活性,减轻氧化应激损伤,为组织修复创造条件^[64,71]。

②促进血管生成、改善微循环类成分。糖尿病创面血管生成障碍是愈合延迟的关键环节。多种中药成分通过激活PI3K/Akt信号通路及其下游血管生成相关因子,有效促进血管新生。三七皂苷可经PI3K/Akt/mTOR信号通路促进成纤维细胞增殖与胶原生成,并上调VEGF、PDGF、成纤维细胞生长因子(FGF)等血管生成因子表达,同时降低TNF- α 和

IL-6水平,兼具促血管与抗炎作用^[62]。人参皂苷具有抗氧化、抗炎等多种药理作用^[72],能通过激活PI3K/Akt信号,促进70 kDa核糖体蛋白S6激酶(p70s6K)活化,并经由缺氧诱导因子-1 α (HIF-1 α)介导的VEGF表达刺激血管生成,从而加速皮肤溃疡愈合^[65]。茯苓三萜提取物能促进巨噬细胞向M2型极化,降低炎症因子表达,同时激活p-PI3K和p-Akt,上调血小板内皮细胞黏附分子-1(CD31)和VEGF mRNA,促进内皮细胞迁移,利于血管新生^[66]。西青果提取物能促进人脐静脉内皮细胞(HUVECs)的增殖、迁移和管腔形成,其机制与激活PI3K/Akt和HIF-1 α 信号通路,进而加速糖尿病创面血管生成密切相关^[67]。

③调节自噬、促进组织修复类成分。自噬紊乱在糖尿病创面愈合障碍中扮演重要角色,部分中药成分通过调节PI3K/Akt/mTOR轴影响自噬,促进组织修复。裸花紫珠主要化学成分包括黄酮类化合物、挥发油、酚萜类等^[73],对创伤性伤口具有抗炎、止血和加速伤口愈合的作用^[74-75],其提取物能显著促进糖尿病创面大鼠的愈合,研究显示其可上调创面组织中胰岛素样生长因子-1(IGF-1)、IGF-1R、PI3K、Akt、内皮型一氧化氮合酶(eNOS)、VEGF及其受体VEGFR2的mRNA和蛋白表达,提示其可能通过IGF-1/PI3K/Akt信号通路发挥治疗作用,该通路也与自噬调控存在交叉^[25]。

综上所述,中药有效成分虽来源各异,但均可通过对PI3K/Akt这一核心信号枢纽的多靶点干预,在抑制炎症、抗氧化、促进血管生成及调节细胞功能等不同层面协同发挥作

用,充分体现了中药多成分、多通路整合调控的治疗优势,为中药现代化研究及其在糖尿病创面治疗中的应用提供了科学依据。

4.2 中药复方调控PI3K/Akt信号通路治疗DW 在中药有效成分研究基础上,复方制剂因其多成分、多靶点的整合调节作用,更契合DW“虚、瘀、毒”交织的复杂病机特点,展现出整体调控的优势。诸多临床常用复方通过多途径协同激活PI3K/Akt信号通路及其下游网络,在扶正补虚、化瘀通络、清热解毒等不同层面发挥综合疗效,从而有效促进创面愈合。以下将结合代表性复方,依据其核心治法与作用特点,分为益气扶正活血、活血化瘀通络、清热解毒3类进行系统论述。中药复方调控PI3K/Akt信号通路治疗DW见增强出版附加材料^[76-91]。

①益气扶正活血类中药复方。此类复方针对DW“正气亏虚”之本,通过益气以扶助正气,来推动血液运行,为组织修复提供物质基础与动力。黄芪阳和汤以温阳补血、散寒通滞为法,能显著上调p-PI3K、p-Akt及核转录因子- κ B抑制蛋白 α (I κ B α)蛋白表达,上调组织经皮氧分压(TcpO₂)、血清VEGF、HIF-1 α 表达,同时抑制p-NF- κ B、p65,通过调控PI3K/Akt/NF- κ B轴抑制炎症、促进血管新生^[77]。益气化瘀方以益气化瘀生肌为法,可通过调节PI3K/Akt/mTOR信号通路,降低血糖,改善DW大鼠周围神经病变,加速创面愈合^[78]。补虚化瘀汤与回阳生肌汤亦属此类,前者通过网络药理学从5个中药中筛选出106个活性成分,构建了活性成分-靶点(ACT)网络。发现多个成分(如槲皮素、木犀草素等)可作用于多个靶点,而多个靶点也可被多个成分共同调控。分子验证关键成分与靶点的结合,对12个关键成分与8个关键靶点进行分子对接,发现木犀草素和槲皮素与多个靶点有较强亲和力,复方激活PI3K/Akt/eNOS信号通路促进血管生成和伤口愈合^[80];后者则能提升血清EGFR水平,激活PI3K/Akt/mTOR信号通路,促进慢性创面表皮细胞增殖^[79]。芪柏愈疡油具有益气活血、燥湿解毒、敛疮生肌的功用,能通过激活PI3K/Akt信号通路,上调HIF-1 α 的表达,提高其下游基因VEGF、PDGF、碱性成纤维细胞生长因子(bFGF)、表皮生长因子(EGF)的表达水平,降低组织中IL-1 β 、IL-6、TNF- α 的表达,从而促进血管生成,加速创面愈合^[81]。当归黄芪汤具有益气补血、托毒生肌的功用。临床试验研究发现,运用贝前列素钠片联合当归黄芪汤治疗,可以明显降低治疗组患者体内晚期氧化蛋白产物(AOPP)及丙二醛(MDA)水平^[92]。既往研究表明黄芪甲苷可通过调节PI3K/Akt/Nrf2信号通路影响细胞氧化,增强SOD活性^[71],考虑贝前列素钠片联合当归黄芪汤可能通过黄芪甲苷显著改善DW患者AOPP、MDA及SOD,减轻氧化应激,改善局部疼痛感,促进破溃伤口的愈合。生肌化瘀方具有益气生肌、活血化瘀的功用。高效液相色谱-质谱联用技术(HPLC-MS)和分子对接表明,筛选出2个核心单体,毛蕊异黄酮(Cal)和去氢丹参新酮(DHT)具有很强的靶向性整合素 α 6亚基(Itga6)和血小板反应蛋白1(Thbs1)。mRNA和蛋白水平表明,Itga6和Thbs1是糖尿病创面PI3K/Akt信号通路的重要上游调节因子,体外

实验表明,Cal、DHT及其配方显著提高了甲基乙二醛(MGO)诱导的人永生化角质形成细胞(HaCaT)细胞中Itga6、Thbs1、PI3K和Akt的水平。结果表明,生肌化瘀方可能通过PI3K/Akt信号通路治疗DW^[76]。

②活血化瘀通络类中药复方。本类复方紧扣“瘀血阻络”之核心病机,通过活血化瘀以畅通气血,改善局部微循环。脑心通胶囊集多味活血虫药于一方,能显著促进PI3K/Akt/eNOS信号通路磷酸化,增加肉芽组织面积、上皮化及伤口周围血管密度,体现“益气活血、化瘀通络”之效^[82]。糖周宣痹通脉方以温阳散寒、逐瘀通脉为长,可上调PI3K、Akt、VEGF蛋白及mRNA表达,下调IL-6、TNF- α 水平,促进肉芽组织与毛细血管新生,加速愈合^[83]。消肿止痛合剂与破瘀汤亦为活血代表方,前者通过上调p-PI3K、p-Akt、p-mTOR蛋白表达,下调组织中TNF- α 、IL-1 β 、IL-6水平,抑制内皮细胞过度自噬与炎症^[86,93];后者则能上调p-PI3K、p-Akt、p-mTOR及VEGFR2表达,降低炎症,促进缺血溃疡组织血管新生^[85]。此外,复黄软膏这类外用膏药,通过调控PI3K/Akt信号通路,下调TNF- α 、IL-6表达、上调增殖细胞核抗原(PCNA)表达,并在减轻组织炎症并加速角质形成细胞增殖发挥重要作用^[84]。

③清热解毒类中药复方。此类复方针对“毒邪内蕴”之标实,通过清热解毒以净化创面,控制感染,为组织修复创造条件。十敛散联合内服舒脉胶囊以外用化瘀解毒、内服益气化浊为法,可激活PI3K/Akt/松弛素(Relaxin)/爱帕琳肽(Apelin)信号通路,下调IL-6、IL-1 β 等炎症因子,上调VEGF、Relaxin、Apelin水平等表达,促进肉芽组织与毛细血管生成^[87]。湿润烧伤膏以清热解毒、生肌止痛为法,能通过PI3K/Akt/叉头框蛋白O1(FoxO1)信号通路调控EMT过程,影响上皮钙黏蛋白(E-cadherin)、闭合蛋白1(Claudin1)及波形蛋白(Vimentin)表达,促进再上皮化^[88]。三黄消炎方集多种清热药于一方,可通过干预PI3K/Akt等炎症通路,调节CD4阳性辅助性T淋巴细胞(CD4⁺T)细胞,抑制17型辅助性T细胞(Th17)细胞分化,减轻炎症并促进愈合^[89]。参黄六味散兼有活血生肌、祛湿解毒之效,经网络药理学发现其复方多成分协同促进愈合,其机制与抑制晚期糖基化终末产物(AGE)/晚期糖基化终末产物受体(RAGE)信号通路、激活PI3K/Akt/eNOS/HIF-1 α 轴,促进抗菌与血管生成有关^[91]。此外,紫朱软膏这类外用清热解毒类复方,通过调控PI3K/Akt信号通路,在抗炎、促血管生成及加速上皮化方面发挥重要作用^[90]。

综上所述,中药复方基于“虚、瘀、毒”病机,分别从益气养阴扶正、活血化瘀通络、清热解毒3类治法入手,通过多靶点、整体性调控PI3K/Akt信号通路及其下游网络,在DW愈合中发挥多环节、协同整合的治疗作用,充分体现了中医药“病证结合、以法统方”的辨治优势与科学内涵。

5 中药调控PI3K/Akt通路的理论内涵与用药特色

基于前述中药有效成分及复方通过调控PI3K/Akt信号通路促进DW愈合的作用机制,可系统总结出中医药干预具有多维度、多层次的整体调节规律,且与中医“虚、瘀、毒”核

心病机高度契合。DW属于本虚标实之证,气阴两虚为其根本,瘀血阻络与毒邪内蕴为其标实。正气亏虚,元气不充,则无力推动血行、濡养肌肤,致使创面久不收敛;瘀血既为病理产物,又可作为继发性致病因素,阻滞络脉,妨碍新肉生长;毒邪内涵丰富,既包括高糖化热酿浊之内生毒邪,又涵盖创面染毒之外邪侵袭,毒瘀交结,损络腐肉,进一步加重组织损伤与现代病理中炎症、氧化应激及细胞功能障碍等过程相对应。PI3K/Akt通路作为细胞存活、增殖与代谢的核心信号轴,其功能抑制可视为“虚、瘀、毒”病机在微观分子层面的具体体现。而中医药则以“病-证-法-方”一体化的诊疗思路,通过“扶正补虚以治本、活血化瘀以通络、清热解毒以祛邪”的治则,实现对PI3K/Akt信号通路的多靶点、双向调节,彰显了整体观指导下的辨治优势。具体而言,中药干预该通路表现出三类主要规律,并与中医治法相对应。

5.1 益气扶正类中药调控PI3K/Akt信号通路——治其本虚 此类中药以黄芪、人参、黄精为代表,其活性成分如黄芪甲苷IV、人参皂苷等,针对DW“正气亏虚”之本质。中医理论认为,“正气存内,邪不可干”,“精气夺则虚”。消渴日久,气阴耗伤,正气亏虚,无力抗邪、生肌长肉,是创面难愈之本。现代研究表明,益气类中药能显著改善高糖微环境下的PI3K/Akt信号通路抑制状态。例如,黄芪甲苷IV可促进PI3K/Akt/mTOR信号通路活化,进而上调创面组织CD31、VEGF表达,促进血管新生与胶原沉积^[64];其亦可能通过调节PI3K/Akt/Nrf2轴增强抗氧化酶SOD活性,减轻氧化应激^[71]。人参皂苷则可通过激活PI3K/Akt信号通路,促进其下游p70S6K的活化,并经由HIF-1 α 介导的VEGF表达刺激血管生成,从而加速创面愈合^[65]。在复方层面,黄芪阳和汤融温阳补血与益气通滞于一方,能显著上调p-PI3K、p-Akt及I κ B α 蛋白表达,提升组织TepO2及血清VEGF、HIF-1 α 水平,同时抑制p-NF- κ B、NF- κ B p65,通过调控PI3K/Akt/NF- κ B轴抑制炎症、促进血管新生。益气化瘀方以益气化瘀生肌为法,可调节PI3K/Akt/mTOR信号通路,改善DW大鼠周围神经病变,加速创面愈合。此治法紧扣“虚”之病机,以“扶正补虚”为法,选用益气扶正活血之方药,其核心机制在于激活PI3K/Akt“枢纽”通路,增强胰岛素受体底物敏感性,改善细胞能量代谢,促进细胞增殖与迁移,从而恢复机体自我修复潜能,体现了“扶正以生肌”的深刻内涵。

5.2 活血化瘀通络类中药调控PI3K/Akt信号通路——治其瘀阻 此类中药以丹参、三七、当归、赤芍为代表,其活性成分如三七皂苷等,针对“瘀血阻络”之核心病理环节。中医理论强调,“久病必瘀”,“瘀血不去,新血不生”,瘀血阻滞络脉,气血运行不畅,肌肤失养,则创面难以愈合。活血化瘀通络类中药能有效逆转PI3K/Akt信号通路的功能抑制,改善微循环与组织修复。研究发现,三七皂苷可通过PI3K/Akt/mTOR信号通路促进成纤维细胞增殖和胶原蛋白生成,同时上调VEGF、PDGF等血管生成因子表达,促进新血管形成,加速DW愈合^[62]。复方如脑心通胶囊(益气活血)可通过促进PI3K/Akt/eNOS信号通路的磷酸化,增加伤口周围血管密度和VEGF表达,从而促进创面愈合^[82];糖周宣痹通脉方(温

阳通脉化瘀)可通过调控PI3K/Akt信号通路,上调VEGF、IGF-1表达,促进血管新生^[83]。此法对应于“瘀”之病机,以“活血化瘀通络”为治则,其分子生物学基础在于激活PI3K/Akt/eNOS、PI3K/Akt/HIF-1 α /VEGF等下游信号轴,促进血管内皮细胞功能、增加肉芽组织中胶原沉积与上皮再生,从而修复组织缺损,深刻诠释了中医“瘀去新生”“通络生肌”理论的科学实质。

5.3 清热解毒类中药调控PI3K/Akt通路——治其毒蕴 此类中药以黄连、黄柏、栀子、大黄为代表,其活性成分如栀子苷、山竹子素等,针对“内毒外邪交织”之标实。中医认为,“毒损络脉,腐肉为脓”,毒邪炽盛,进一步损伤经络,腐筋蚀骨,是创面溃烂、脓液滞留、炎症持续的重要原因。清热解毒类中药主要通过抑制过度活化的PI3K/Akt/NF- κ B炎症信号轴,发挥抗炎、抗氧化及抑制细胞焦亡等作用。例如,栀子苷能显著降低DW组织中TNF- α 、IL-1 β 和IL-6等促炎因子水平,其机制与促进PI3K和Akt蛋白磷酸化,进而抑制NF- κ B等炎症信号转导密切相关^[61]。山竹子素则可通过下调PI3K/Akt/NF- κ B信号通路,抑制巨噬细胞分泌炎症细胞因子,改善血管生成并抑制细胞焦亡,从而促进DW愈合^[63]。复方如三黄消炎方,网络药理学提示其可通过干预PI3K/Akt等炎症通路,抑制Th17细胞分化,增强DW愈合^[89]。参黄六味散其机制与抑制AGE/RAGE信号通路、激活PI3K/Akt/eNOS/HIF-1 α 轴,促进抗菌与血管生成有关。此治法针对“毒”之病机,以“清热解毒”为法,其现代药理学机制在于精准调控PI3K/Akt/NF- κ B这一关键节点,下调TNF- α 、IL-6等促炎因子表达,减轻氧化应激与细胞焦亡,清除微环境中的毒害因素,为正气来复与新肉生长创造洁净的创面环境,充分体现了“祛邪以扶正”“解毒以护络”的治疗逻辑。

综上所述,PI3K/Akt信号通路作为连接“虚、瘀、毒”病机与现代分子病理的关键桥梁,不仅为中医药治疗DW提供机制阐释,也凸显了中医“以证统病、法随证立、方证相应”的整体思维在现代医学研究中的独特价值。临床常用复方多融合上述3类治法,体现中医药“标本兼治、复方协同”的整体调节特色。其通过多成分、多靶点作用,对PI3K/Akt信号通路实施精细的双向调控:既促进修复性细胞增殖与血管生成,又抑制过度炎症与凋亡;既增强生长因子信号,又改善胰岛素抵抗与自噬紊乱,从而在多维病理环节系统纠正DW的失衡状态。这种“病机-治法-方药-通路”一体化的研究模式,既深化了对中药复方系统调控机制的理解,也为中药新药研发与中西医结合治疗提供了理论依据和转化路径。

6 结语与展望

DW愈合障碍是糖尿病严重的并发症之一,其修复过程涉及多细胞、多通路的精密调控。PI3K/Akt信号通路作为调控细胞代谢、增殖与存活的核心通路,在DW修复中扮演关键角色。研究表明,该通路活性下降与高糖所致的炎症反应、氧化应激、细胞凋亡、自噬紊乱及血管生成障碍等病理过程密切相关。目前,诸多中药有效成分及复方可通过激活PI3K/Akt信号通路,有效减轻炎症、抑制凋亡、调节自噬并促进血管新生,从而协同促进创面愈合,体现中医药多成分、多

靶点的整合调控优势。尤其值得注意的是,中医药在干预DW过程中体现出“病-证-法-方”一体化的整体调节特色。基于“虚、瘀、毒”交互为患的核心病机,益气活血、温阳通脉、清热解毒等治法分别从不同维度恢复PI3K/Akt信号通路功能,不仅着眼于局部创面修复,更注重整体气血调和,彰显中医药“标本兼治”的治疗理念。

然而,该领域仍存在一些问题,多数研究局限于动物与细胞实验,临床转化证据不足;复方活性成分群及其协同机制尚未明确;PI3K/Akt与其他信号通路的交互作用有待深入解析。未来研究应侧重以下方向,积极开展多中心、大样本随机对照试验,验证中药临床疗效与安全性;构建“病证结合”的动物模型,来深入探究中药复方的协同作用机制;着力于中药外用新型制剂(如智能响应水凝胶、纳米纤维敷料)的开发与中西医结合治疗模式的探索,以推动临床转化;结合系统药理学、代谢组学及蛋白组学等技术,精准鉴定复方有效成分群并阐明其协同机制;从气血理论、络病理论等中医理论层面深化对DW病机与治法的认识,实现“临床-基础-临床”的转化闭环。对比当前治疗策略可见:西药靶向治疗具有机制明确、效力集中的优势,但面对DW多环节失调的复杂病理,常显单一,且存在耐药与不良反应风险。而中医药通过“多成分-多靶点”模式,在调控PI3K/Akt核心通路的同时,协同干预NF- κ B、HIF-1 α 等交叉网络,实现了对炎症、血管新生等多维病理环节的整体调节。然而,中药也面临成分复杂、机制不清的挑战。未来研究应阐明中药网络化机制的基础上,推动中西医策略的深度融合与创新。综上所述,以PI3K/Akt信号通路为枢纽阐释中医药促DW愈合的机制,不仅有助于揭示其现代科学内涵,也为研发靶向药物和制定中西医结合治疗方案提供新思路。随着交叉学科发展与精准医学理念的深入,中医药在DW治疗领域具有广阔的临床转化与应用前景。

[利益冲突] 本文不存在任何利益冲突。

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