

· 综述 ·

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PINK1/Parkin 信号通路介导的线粒体自噬在代谢相关脂肪性肝病中的作用及靶向治疗研究进展

朱胜金¹, 朱小灯², 李开杨³, 杨梅¹, 吴娴⁴

1 贵州中医药大学第二附属医院检验科, 贵阳 550001

2 北京积水潭医院贵州医院检验科, 贵阳 550014

3 贵州中医药大学第二临床医学院, 贵阳 550002

4 贵州省人民医院产前诊断中心, 贵阳 550002

通信作者: 朱小灯, 271501247@qq.com (ORCID: 0009-0008-5821-5772); 李开杨, 1592877812@qq.com (ORCID: 0009-0000-3276-6295)

摘要: 代谢相关脂肪性肝病(MAFLD)发病机制复杂,而线粒体自噬参与了MAFLD的发生发展,在肝脏代谢途径和信号网络中起着关键作用。线粒体自噬受多种途径的调控,同源性磷酸酶张力蛋白诱导激酶1(PINK1)/帕金蛋白(Parkin)途径被认为是调节线粒体自噬的主要途径,PINK1/Parkin介导的线粒体自噬可调节脂质代谢、炎症及纤维化,缓解MAFLD的进展。本文综述了PINK1/Parkin介导的线粒体自噬在MAFLD中的作用及靶向治疗的研究进展,以期防治MAFLD提供理论依据和思路。

关键词: 代谢相关脂肪性肝病; 线粒体自噬; PINK1/Parkin 信号通路

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Role of mitophagy induced by the PTEN-induced kinase 1/Parkin signaling pathway in metabolic associated fatty liver disease and related advances in targeted therapies

ZHU Shengjin¹, ZHU Xiaodeng², LI Kaiyang³, YANG Mei¹, WU Xian⁴

1. Department of Clinical Laboratory, The Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 550001, China; 2. Department of Clinical Laboratory, Guizhou Hospital, Beijing Jishuitan Hospital, Guiyang 550014, China;

3. The Second Clinical Medical School of Guizhou University of Traditional Chinese Medicine, Guiyang 550002, China; 4. Prenatal Diagnosis Center, Guizhou Provincial People's Hospital, Guiyang 550002, China

Corresponding authors: ZHU Xiaodeng, 271501247@qq.com (ORCID: 0009-0008-5821-5772); LI Kaiyang, 1592877812@qq.com (ORCID: 0009-0000-3276-6295)

Abstract: Metabolic associated fatty liver disease (MAFLD) has a complex pathogenesis, and mitophagy is involved in the development and progression of MAFLD and plays a key role in liver metabolic pathways and signaling networks. Mitophagy is regulated by a variety of pathways, and the PTEN-induced kinase 1 (PINK1)/Parkin pathway is considered the main pathway for regulating mitophagy. Mitophagy mediated by the PINK1/Parkin pathway can regulate lipid metabolism, inflammation, and fibrosis and delay the progression of MAFLD. This article reviews the role of mitophagy mediated by the PINK1/Parkin pathway in MAFLD and the research advances in targeted therapy, in order to provide theoretical bases and ideas for the prevention and treatment of MAFLD.

Key words: Metabolism-Associated Fatty Liver Disease; Mitophagy; PINK1/Parkin Signaling Pathway

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非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)/代谢相关脂肪性肝病(metabolism-associated fatty liver disease, MAFLD)是肝细胞中脂肪过量沉积而导致的慢性肝病^[1]。NAFLD影响约25%的一般人群和50%以上的代谢异常患者,是慢性肝病及其并发症的一个新病因^[2],2020年国际专家小组提出将NAFLD更名为MAFLD^[3]。肝细胞中过量的脂质蓄积会导致氧化应激和脂毒性,并通过多种机制促进线粒体功能障碍,线粒体损伤引发肝细胞死亡或功能障碍是MAFLD最重要的特征之一^[4]。因此,保护线粒体免受氧化应激和脂毒性损伤对于延缓或逆转MAFLD的进展至关重要。

线粒体自噬是一种高度保守的选择性自噬过程,可维持线粒体的质量和数量。通过线粒体自噬,细胞可以应对线粒体应激或氧化应激,使损伤保持可控,从而使细胞存活^[5]。越来越多的证据表明,线粒体自噬可调节肝脏脂质代谢、炎症及纤维化,缓解MAFLD^[6]。线粒体自噬调控途径众多,同源性磷酸酶张力蛋白诱导激酶1(PINK1-induced putative kinase protein 1, PINK1)/帕金森蛋白(Parkin)作为调节线粒体自噬的主要途径,参与MAFLD的发生发展^[7-8]。因此,积极探讨PINK1/Parkin介导的线粒体自噬在MAFLD中的作用及靶向治疗的研究现状具有重要意义,以期防治MAFLD提供参考。

1 线粒体自噬

线粒体是细胞内产生能量的细胞器,是有氧呼吸的主要场所,被称为“发电站”,参与机体内各种关键细胞过程。线粒体自噬是一种特殊形式的自噬,在生理条件下,线粒体自噬可以有效去除功能受损的线粒体,维持细胞内钙稳态、细胞信号转导和三磷酸腺苷合成,并降低活性氧(ROS)水平和氧化应激损伤^[9]。在应激条件下,如细胞内缺氧、营养缺乏、细胞衰老、创伤性损伤时会导致线粒体损伤或功能障碍,从而诱导线粒体自噬^[10-11]。机

体为了维持线粒体网络的稳定和保持细胞内环境的稳定,使用自噬机制来选择性地包裹和降解细胞内受损或功能障碍的线粒体^[12-13],这个过程主要由四个阶段组成^[14]:(1)受损的线粒体去极化,线粒体膜电位($\Delta\Psi_m$)消失:在缺氧、营养缺乏、细胞衰老和其他外界应激的作用下,线粒体膜电位消失,这是发生线粒体自噬的先决条件。(2)自噬体包裹线粒体,形成线粒体自噬体。(3)线粒体自噬体与溶酶体融合。(4)线粒体内容物被溶酶体降解:溶酶体或液泡酸水解酶流入自噬体降解线粒体,内容物循环利用(图1)。越来越多的证据表明,线粒体自噬作为一种急性组织应激反应下的细胞保护机制,在代谢性疾病、神经退行性疾病和癌症等疾病中起着重要作用。

2 PINK1/Parkin 介导的线粒体自噬

线粒体自噬是一种选择性识别和清除受损或多余线粒体的特殊自噬形式,与一般自噬具有相同的基本特征和核心蛋白。自噬体吞噬线粒体的特异性通过不同的机制实现,线粒体自噬途径主要有PINK1/Parkin轴依赖性线粒体自噬、受体介导的线粒体自噬、FUN14结构域1介导的线粒体自噬、Bcl-2/腺病毒E1B19kDa相互作用蛋白3介导的线粒体自噬、Bcl-2家族蛋白Bcl-rambo介导的线粒体自噬等^[15-16]。而PINK1/Parkin是目前研究最广泛的线粒体自噬途径。

PINK1是一种被导入健康线粒体并持续降解的线粒体丝氨酸-苏氨酸激酶,由帕金森病隐性家族6型(recessive familial type 6 of Parkinson's disease, PARK6)基因编码的高度保守的线粒体蛋白,参与许多细胞生理过程的调节,尤其是线粒体功能的调节,可保护细胞免受应激诱导的线粒体功能障碍^[17]。Parkin是一种E3泛素连接酶,由PARK2基因编码的蛋白质,具有调节磷酸化位点的N末端泛素样(N-terminal ubiquitin-like, Ubl)

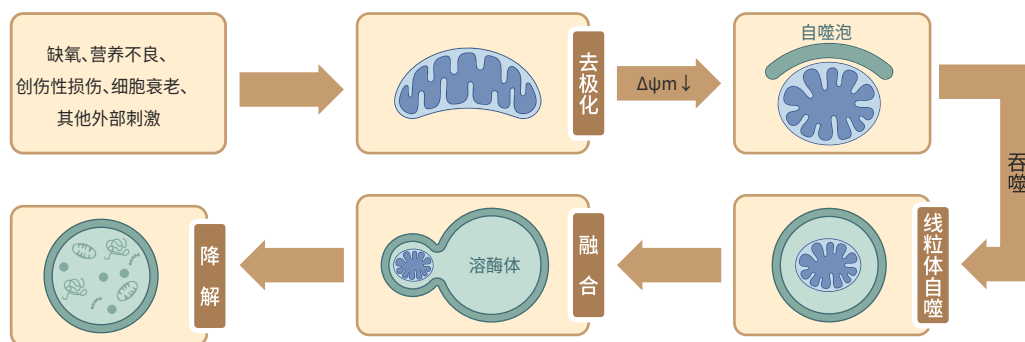


图1 线粒体自噬途径

Figure 1 Mitophagy pathway

结构域,负责连接Ub分子和底物蛋白,带有Ub标签的底物蛋白被蛋白酶体识别^[18]。在PINK1-Parkin调节通路中包含三个关键组件:PINK1、Parkin、泛素链,PINK1为线粒体损伤传感器,Parkin为信号放大器,泛素链为信号效应器,三者共同决定受损的线粒体如何激活线粒体自噬^[19]。正常情况下,PINK1稳定在线粒体外膜上并感知线粒体健康状况,而在线粒体内表达较低。当线粒体受损时, $\Delta\Psi_m$ 降低,PINK1进入线粒体内膜受阻,大量积累在线粒体外膜上^[20]。一旦被激活,PINK1磷酸化Ser65位点上的泛素,磷酸化泛素(pUb)作为Parkin的线粒体受体,招募Parkin从细胞质转移到线粒体外膜上并将其在Ser65位点上磷酸化^[21]。活化的Parkin泛素化线粒体外膜蛋白进一步磷酸化,从而为PINK1介导的泛素磷酸化创造更多底物,反过来又导致Parkin募集^[22]。pUb与Parkin结合形成Parkin-Ub复合物,用于标记受损的线粒体,随后,可溶性自噬受体(如衔接蛋白p62)连接Parkin-Ub复合体和微管相关蛋白1轻链3(microtubule-associated protein 1 light chain 3, LC3)蛋白,使自噬体能够吞噬受损的线粒体^[23](图2)。受损线粒体周围的自噬体闭合最终与溶酶体融合并发生降解。

3 PINK1/Parkin 介导的线粒体自噬与 MAFLD

MAFLD的发病机制复杂,生活方式、遗传易感性、脂质代谢紊乱、胰岛素抵抗、脂毒性、线粒体功能障碍、氧化应激、内质网应激、炎症、先天免疫调节异常和肠道微生物群紊乱等参与其发生发展^[24-26]。而线粒体功能障碍被认为是MAFLD的一个标志,在肝脏代谢途径和信号网络中起着关键作用^[27]。研究表明,诸如线粒体自

噬、氧化应激、分化和质量控制等因素不同程度地影响线粒体功能,从而促进肝脏脂肪积累和损伤^[28]。肝脏通过线粒体自噬去除受损的线粒体被广泛认为是MAFLD长期发展过程中的一种保护机制^[29]。

3.1 改善脂质代谢 Undamatla等^[30]建立肝脏特异性Prkn敲除小鼠品系(LKO),发现肝脏特异性Prkn敲除LKO小鼠在高脂饮食喂养期间会出现更严重的脂肪变性,肝脏中的线粒体呼吸能力降低,胰岛素抵抗和MAFLD标志物增加。提示Parkin介导的线粒体自噬在体内可维持线粒体完整性,对MAFLD具有保护作用。在油酸诱导的MAFLD细胞中,上调PARK2可以增强PINK1表达,从而加速自噬体的形成,表现为LC3在自噬体膜上的积累,从而逆转MAFLD细胞病变状态,而下调PARK2表达则加重MAFLD细胞病变状态,表明PINK1/PARK2介导的线粒体自噬有助于改善油酸诱导的MAFLD^[31]。

3.2 减轻炎症反应 研究表明,促进PINK1/Parkin介导的线粒体自噬,可以抑制由ROS和线粒体DNA触发的炎症反应,从而减轻肝损伤^[32]。在体内外高脂环境中,髓系GSK3 β 缺失促进线粒体上PINK1的表达,并通过磷酸化泛素蛋白激活Parkin,促进线粒体自噬的发生,从而减少巨噬细胞中ROS的产生和核苷酸结合寡聚化结构域样受体蛋白3(NOD-like receptor protein 3, NLRP3)炎症小体的激活,减轻肝脏的炎症反应^[33]。Zhang等^[34]通过高脂肪/高热量饮食喂养C57BL/6小鼠,第6周时,小鼠肝组织PINK1、Parkin蛋白水平升高,表明在脂肪变性早期阶段线粒体自噬活性增强;12周时,PINK1、Parkin蛋白水平以及PARK2和PINK1 mRNA水平开始下降;24周时,

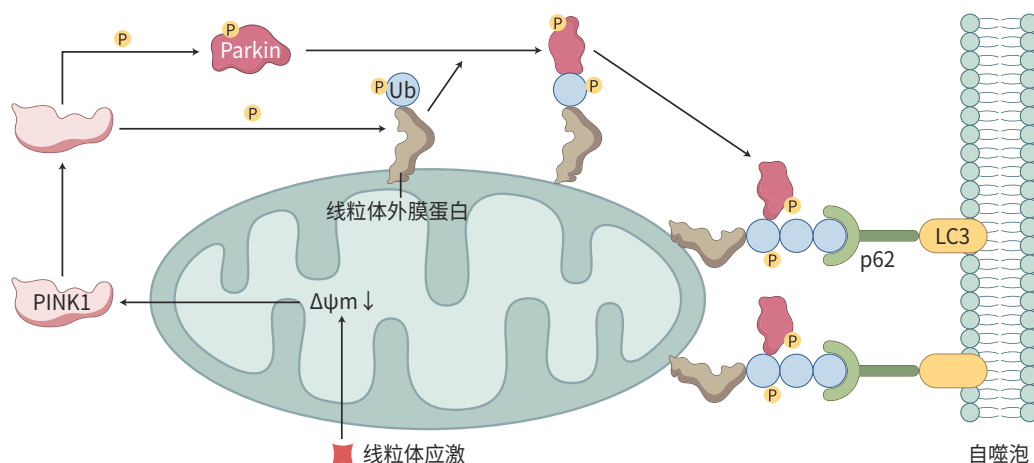


图2 PINK1/Parkin介导的线粒体自噬途径

Figure 2 PINK1/Parkin-mediated mitophagy pathway

p62蛋白水平显著升高,而PARK2和PINK1 mRNA水平受到显著抑制。由此提示,PINK1/Parkin介导的线粒体自噬活性在MAFLD早期的表达可能增强,随着脂肪变性程度和炎症的增加自噬活性逐渐下降。

3.3 逆转肝纤维化 Ding等^[35]研究发现,在肝纤维化逆转过程中,PINK1/parkin介导的线粒体自噬在肝星状细胞中增强,并促进其凋亡,抑制线粒体自噬可增强小鼠肝星状细胞的活化,从而加重纤维化。表明激活PINK1/Parkin介导的线粒体自噬可逆转肝纤维化。

综上,PINK1/Parkin介导的线粒体自噬在MAFLD发生发展中扮演重要角色,调控PINK1/Parkin信号通路可能是治疗MAFLD的潜在靶点。但目前的研究较少且尚未深入,PINK1/Parkin介导的线粒体自噬在MAFLD不同阶段的作用机制以及是否存在下游信号通路仍有待进一步探索。

4 调控PINK1/Parkin介导的线粒体自噬治疗MAFLD

4.1 生活方式干预PINK1/Parkin介导的线粒体自噬治疗MAFLD

生活方式是MAFLD发病最密切的影响因素^[36]。生活方式干预(如饮食干预、体育锻炼等)通常被视为MAFLD治疗的基石,可有效改善与MAFLD相关的许多症状^[37]。因此,生活方式干预对于阻止MAFLD肝脏病变的进展具有重要意义。

4.1.1 饮食干预 玉米肽是一种以玉米蛋白粉为原料,通过酶解或微生物发酵制备的具有结构新颖、分子量低、营养价值高的新型食品^[38]。在高脂饮食诱导的NAFLD大鼠的肝脏和游离脂肪酸诱导的HepG2细胞中,PINK1和Parkin蛋白水平及自噬相关蛋白ATG7、LC3 I/II表达降低,p62表达升高,而玉米肽干预后被逆转,进一步研究玉米肽在PINK1/Parkin介导的线粒体自噬调节脂质代谢中的作用,敲低HepG2细胞中PINK1的表达,发现PINK1的缺失消除了玉米肽对脂质积累的保护作用并抑制了线粒体自噬,表明玉米肽通过PINK1/Parkin介导的线粒体自噬改善NAFLD细胞损伤,改善线粒体功能障碍和脂质积累^[39]。

4.1.2 运动干预 运动是治疗MAFLD的一种有效方式。Zou等^[40]研究表明,在NAFLD斑马鱼模型中,肝脏PINK1/Parkin通路受到抑制,线粒体自噬体数量减少,游泳运动激活了Parkin蛋白表达并抑制p62表达,提示游泳运动减轻了高脂饮食诱导的NAFLD斑马鱼模型的线粒体形成。证实了运动可能是靶向肝细胞线粒体自噬

治疗NAFLD的有效策略。

4.1.3 运动联合饮食干预 运动联合饮食干预可通过不同的分子途径促进脂肪自噬,改善脂质代谢,延缓肝脏衰老^[41]。Rosa-Caldwell等^[42]研究不同的减重方式对NAFLD肝脏线粒体自噬的影响,发现饮食减重组、饮食联合运动减重组肝组织中PINK1、Parkin表达水平升高,p62表达水平下调,饮食联合运动减重组总LC3水平增加。结果提示,高脂肪饮食会导致线粒体自噬标志物的破坏,饮食联合运动干预能显著增强肝脏线粒体自噬,从而改善MAFLD。

4.2 中医药干预PINK1/Parkin介导的线粒体自噬治疗MAFLD

中医药注重整体调控和辨证论治,在治疗MAFLD方面有独特的优势和良好的发展前景。中药活性成分、中药复方具有多靶点、多途径的优点,正契合MAFLD的治疗需要。

4.2.1 中药活性成分 矢车菊素-3-O-葡萄糖苷是一种存在于多种水果和蔬菜中的膳食花青素,具有抗氧化、抗炎和抗肿瘤等作用^[43]。Li等^[44]研究显示,矢车菊素-3-O-葡萄糖苷能够增强非酒精性脂肪性肝炎(NASH)患者和小鼠肝脏中的自噬通量,增加PINK1/Parkin通路蛋白的表达和线粒体定位,并促进PINK1介导的线粒体自噬以清除受损的线粒体,而敲低肝脏PINK1可消除矢车菊素-3-O-葡萄糖苷诱导的线粒体自噬作用,从而减弱矢车菊素-3-O-葡萄糖苷对氧化应激、NLRP3炎症小体活化、肝脏脂肪变性和葡萄糖代谢的有益作用。橙皮素是柑橘类水果的一种生物活性类黄酮成分,已被证明可以改善NAFLD^[45]。Li等^[46]研究发现,橙皮素可上调PINK1、Parkin、Beclin-1、ATG5蛋白的表达,下调p62蛋白表达,抑制NLRP3炎症小体相关通路蛋白的表达,提示橙皮素通过促进PINK1/Parkin介导的线粒体自噬抑制NLRP3炎症小体的激活,减轻NAFLD炎症损伤,而沉默PINK1基因削弱了橙皮素的这些作用。

4.2.2 中药复方 理中汤出自《伤寒论》,是中医经典名方,由人参、干姜、白术、炙甘草四味药组成,具有温中散寒、健脾益气之功效。孙东琪等^[47]发现,高脂饮食诱导的NAFLD大鼠的PINK1、Parkin、LC3 II表达水平明显下降,理中汤干预后,NAFLD大鼠的PINK1、Parkin、LC3 II表达水平均明显回升,其干预机制可能与激活PINK1/Parkin介导的线粒体自噬有关。皂术茵陈方由皂角、茵陈、炒白术、栀子、大黄五味药组成,具有清热祛湿、祛痰化痰、健脾益气功效。周志佳^[48]建立高脂饮食诱导的NASH

大鼠模型,经皂术茵陈方干预后,肝组织线粒体 PINK1、Parkin、LC3 表达水平显著升高,p62 蓄积水平显著降低,肝脏脂肪变性、脂质代谢紊乱显著改善,表明皂术茵陈方可激活 PINK1/Parkin 介导的线粒体自噬,来维持线粒体的正常稳态,从而缓解肝脂肪变性和脂质代谢紊乱。祛痰活血方是全国名中医孙同郊教授治疗 NASH 的经验方。研究表明,祛痰活血方能够增加 NASH 大鼠肝组织中 PINK1、Parkin 的表达,促进线粒体自噬,其可能通过调控 PINK1/Parkin 信号通路诱导肝细胞自噬,减轻肝细胞炎症及肝组织脂质沉积,从而发挥治疗 NASH 的作用^[49]。

4.3 西药干预 PINK1/Parkin 介导的线粒体自噬治疗 MAFLD 艾塞那肽是首个胰高血糖素样肽-1 受体激动剂,具有改善血糖、脂代谢、胰岛素抵抗和保护 β 细胞功能等多种生物学效应^[50]。Shao 等^[51]研究发现,NAFLD 小鼠模型中自噬体形成所需的关键蛋白 LC3 和 Beclin-1 以及线粒体自噬途径中的重要蛋白 Parkin 的水平显著降低,NLRP3 炎症小体、丙二醛、白介素-1 β 显著升高,艾塞那肽干预后,肝组织 LC3 I / II、Beclin-1、Parkin 的表达以及自噬体的数量显著增加,NLRP3 炎症小体、丙二醛、IL-1 β 明显下调,提示艾塞那肽可以通过增强自噬/线粒体自噬和抑制氧化应激来抑制 NLRP3 炎性小体激活,从而延缓肝脏炎症进展。此外,一项体外研究表明,利拉鲁肽可减轻线粒体功能障碍和 ROS 生成,同时增强 PINK1 介导的线粒体自噬并防止脂质积累^[52]。这些研究表明调控 PINK1/Parkin 介导的线粒体自噬途径是 MAFLD 治疗中有前途的靶点。

5 小结

随着肝脏自噬机制研究的快速进展,研究者们对线粒体自噬在肝脏病理生理学调控中的分子机制的理解显著提高,但肝脏的线粒体自噬途径众多,机制复杂,涉及多种调控因素,具体机制尚未完全阐明。PINK1/Parkin 信号通路介导的线粒体自噬可以有效去除功能受损的线粒体,促进肝脏脂质代谢,改善炎症损伤,在 MAFLD 的发生发展中发挥着保护作用,但 PINK1/Parkin 信号在肝脏中的调控机制尚不十分清楚。PINK1/Parkin 介导的线粒体自噬能否成为 MAFLD 临床诊断、疗效或预后的潜在生物标志物,仍有待进一步探索。未来,深入研究 PINK1/Parkin 介导的线粒体自噬,可能为涉及线粒体功能障碍的 MAFLD 患者提供新的治疗靶点,有助于研发靶向线粒体自噬的新药物。

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读者·作者·编者

《临床肝胆病杂志》对稿件统计学处理的要求

由于来稿中统计学方法误用现象时有发生,为规范报告标准、保证学术质量,本刊特对稿件中统计学处理作如下要求:

1. 研究设计:应明确说明统计研究设计的名称和主要方法。如调查设计应注明属于前瞻性、回顾性或横断面调查。

2. 资料表达与描述:用均数 \pm 标准差($\bar{x} \pm s$)描述近似服从正态分布的定量资料,用几何均数及其标准差描述对数正态分布资料,用中位数描述呈偏态分布的定量资料。用统计表时,要合理安排纵横标目,并将数据的含义表达清楚。用统计图时,所用统计图的类型应与资料性质相匹配,使数轴上刻度值的标法符合数学原则。

3. 统计方法的选择:应根据所采用的设计类型、资料所具备的条件和分析目的选用合适的统计学方法。

(1)对于定量资料:如数据呈正态且方差齐,两组均数的比较一般采用 t 检验,多组均数的比较及多组中的两两均数比较应采用方差分析和具体的两两比较(如 q 检验)等适合的方法,不应盲目套用 t 检验。

(2)对于定性资料:在使用 χ^2 检验时应根据适用条件选择适合的 χ^2 检验,等级分类资料应采用秩和检验或Ridit检验,不应盲目套用 χ^2 检验。对于回归和相关分析,应结合专业知识和散点图选用合适的回归类型,不应盲目套用简单直线回归分析。对具有重复实验数据的回归分析资料,不应简单化处理。

(3)对于多因素、多指标资料,要在一元分析的基础上,尽可能运用多元统计学方法,以便对因素之间的交互作用和多指标之间的内在联系作出全面、合理的解释和评价。应写明所用统计学方法的具体名称(如四格表资料的 χ^2 检验)及统计量的具体值(如 $\chi^2 = 6.45$)。

4. 统计结果的解释和表达:当 $P < 0.05$ 或 $P < 0.01$ 时,应解释为对比组之间的差异有统计学意义,而不是对比组之间具有显著性(或非常显著性)的差异。统计结论只能说明有统计学意义或无统计学意义,而不能说明专业上差异的大小。统计结论只有与专业有机地相结合,才能得出恰如其分、符合客观实际的最终结论。