

· 综述 ·

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基于“虚气留滞”探讨线粒体功能障碍在原发性肝癌中的作用及中医药干预策略

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摘要: 原发性肝癌是全球高发恶性肿瘤, 当前治疗手段有限且疗效存在个体性差异, 亟需探索新的治疗途径。中医学在肝癌治疗中具有独特优势, “虚气留滞”是重要的辨证理论之一。该理论认为, 肝癌的发生发展与气虚、气滞密切相关, 尤其是“虚气留滞”可导致肝脏气血失调, 进而影响肝功能和代谢。近年研究发现, 线粒体在细胞能量代谢、氧化应激和细胞凋亡等方面发挥关键作用, 线粒体功能异常与肝癌的发生和进展密切相关。本文结合“虚气留滞”理论与线粒体功能相关的最新研究, 探讨二者在原发性肝癌中的关联和作用, 总结中医药调节线粒体功能干预原发性肝癌的研究进展, 为未来的临床研究提供参考。

关键词: 肝肿瘤; 气虚; 血瘀气滞; 痰郁; 线粒体; 中医药疗法

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Role of mitochondrial dysfunction in primary liver cancer and related traditional Chinese medicine intervention strategies: An analysis based on “deficient Qi retention and stagnation”

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Abstract: Primary liver cancer is a highly prevalent malignant tumor worldwide, with limited treatment options and individual difference in treatment outcome, and therefore, there is an urgent need to explore new treatment strategies. Traditional Chinese medicine (TCM) has unique advantages in the treatment of liver cancer, and “deficient Qi retention and stagnation” is one of the important syndrome differentiation-based theories. Based on this theory, it is believed that the development and progression of liver cancer are closely associated with Qi deficiency and Qi stagnation, and in particular, “deficient Qi retention and stagnation” can lead to Qi-blood disharmony in the liver, thereby impairing liver function and metabolism. Recent years have shown that mitochondria play a pivotal role in cellular energy metabolism, oxidative stress, and cell apoptosis, and abnormal mitochondrial function is closely associated with the development and progression of liver cancer. With reference to the latest research advances in the theory of “deficient Qi retention and stagnation” and mitochondrial function, this article discusses their association and role in

primary liver cancer and summarizes the research advances in TCM treatment of primary liver cancer by regulating mitochondrial function, in order to provide a reference for future clinical studies.

Key words: Liver Neoplasms; Syndrome of Qi Deficiency; Syndrome of Blood Stasis and Qi Stagnation; Syndrome of Phlegm Depression; Mitochondria; Traditional Chinese Medicine Therapy

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原发性肝癌(以下简称肝癌)是全球范围内常见且致死率较高的恶性肿瘤之一,其发病隐匿、病情复杂且预后差,具有高发病率和高病死率的特点^[1-3]。线粒体作为关键的细胞能量中心,在维持健康和参与疾病进展中扮演核心角色,其功能障碍与肝癌的发生发展密切相关。因此,调控线粒体功能障碍可能成为治疗肝癌的新靶点。研究表明,线粒体功能障碍引发的能量代谢异常和氧化应激失衡是肝癌细胞增殖与转移的关键机制,与中医“虚气留滞”理论高度契合。本文基于“虚气留滞”视角,通过解析气机失调与线粒体功能紊乱的生物学关联,构建“以气治癌”的中医特色治疗框架(图1),以期对肝癌防治提供新思路。

1 从“虚气留滞”理论探析肝癌病机

1.1 “虚气留滞”概念 “虚气留滞”最早见于宋代杨士瀛所撰《仁斋直指方·胀满方论》,原文记载:“虚者,时胀时减,虚气留滞”。其本义为脾气亏虚,推动功能乏力,进而引发脾虚气滞,呈现为脘腹胀满、时胀时减的病理进程。当代医家王永炎院士结合临床实践,对该理论予以

深化,将“虚气留滞”阐释为“元气亏虚,气血失和,气血津液运行失调,形成气滞、痰凝与血瘀”的病理过程,极大地拓展了该理论的内涵。自此,“虚气留滞”理论不再局限于脾虚气滞范畴,而是用以表征以元气亏虚为根本,以气滞、痰凝和血瘀等阻滞为表象,因虚致滞的一系列复杂病理演变进程。这一理论高度凝练了多种常见慢性疾病的病理环节——元气亏虚与气痰瘀阻相互交结,揭示了此类疾病发生发展过程中以虚为本、以滞为标、因虚致滞的时空动态演变规律及其内在因果联系^[4]。

1.2 基于“虚气留滞”探析肝癌的病机 根据其多种临床症状,通常将其归类于中医的“积聚”“黄疸”“臌胀”和“胁痛”等疾病范畴,现代中医则常称之为“肝积”。《内经》有云:“正气存内,邪不可干。”正气亏虚被视为肝癌发生的内在基础。正气作为人体生命活动的根本,具有维持脏腑功能、保障内外平衡和防御外来病邪的重要作用。若正气亏虚,则五脏六腑及三焦功能失调,导致水液代谢障碍;痰湿内蕴,阻滞经络,使气血运行不畅;日久则痰湿与瘀血相互搏结,癌毒积聚不散,最终形成癌

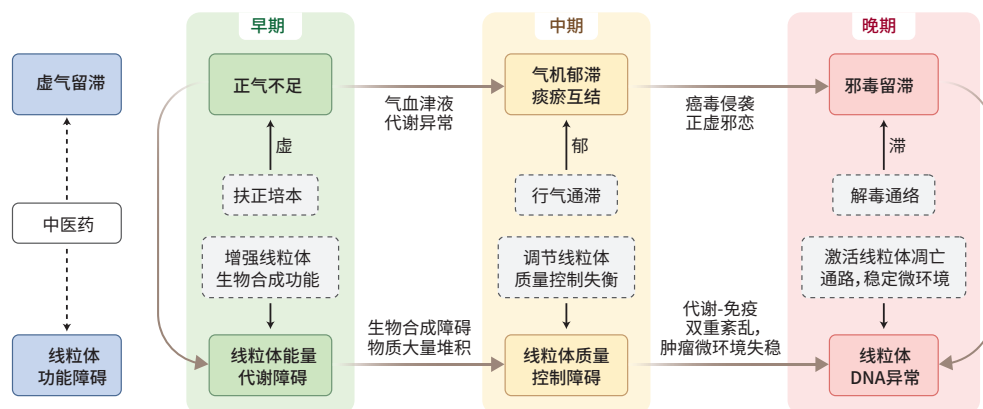


图1 中医药调节线粒体功能干预原发性肝癌的作用机制

Figure 1 The mechanism underlying the regulation of mitochondrial function by traditional Chinese medicine in the intervention of primary liver cancer

积肿块。肝癌起病缓慢,病程较长,其病机常以“虚、郁、滞”为关键因素,其中正气亏虚是发病的根本,气机郁结、邪毒留滞则是致病的外在表现。痰、瘀、毒是肝癌的核心病理产物,而脏毒内结则是疾病进入晚期的显著标志^[5-6]。值得注意的是,癌毒一旦形成,又会进一步耗伤气血,滋生痰瘀,助长毒邪,形成恶性循环。由此可见,“虚气”(正气亏虚)与“留滞”(气滞、痰凝、血瘀和毒蕴)互为因果,共同推动疾病的进展。

2 线粒体功能障碍参与肝癌的发生发展

2.1 线粒体能量代谢障碍 线粒体作为肝细胞的能量核心,通过氧化磷酸化代谢脂质和糖类,生成腺嘌呤核苷三磷酸(adenosine triphosphate, ATP),占细胞能量的90%,同时产生活性氧(reactive oxygen species, ROS)^[7]。过量ROS可引发线粒体通透性转换孔持续开放及跨膜电位($\Delta\psi_m$)消失,导致线粒体肿胀、外膜破裂及ROS爆发,造成线粒体DNA(mitochondria, mtDNA)等氧化损伤(氧化应激)^[8]。研究表明,肝癌的糖代谢重编程与线粒体动态失衡密切相关:动力蛋白相关蛋白1介导的线粒体裂变增强可促进肿瘤增殖、转移及脂肪生成,而融合抑制则会降低癌细胞的耗氧量与ATP水平^[9]。

2.2 线粒体质量控制障碍 线粒体通过持续的融合与分裂维持其形态与功能的稳态,其动态平衡受钙稳态、ATP和ROS水平等调控,形成细胞保护机制。此外,裂变/融合平衡的稳态依赖于生物发生(新生线粒体)和自噬(清除损伤线粒体)的双向调节^[10-11]。质量控制异常表现为动力学失衡、生物发生紊乱及自噬失调,与肝内脂质、ROS蓄积形成互作放大的恶性循环,从而加剧肝损伤进程^[12]。

2.3 mtDNA异常 与核DNA相比,mtDNA缺乏组蛋白和DNA修复系统的保护,容易受到ROS攻击并发生突变。广泛的mtDNA损伤会加剧氧化应激,破坏线粒体呼吸链和能量代谢,从而参与肝脏疾病的发病过程。mtDNA突变和拷贝数变异是肝癌的常见现象^[13]。

3 “虚气留滞”理论与线粒体功能障碍在肝癌中的作用

3.1 “虚气”是导致线粒体功能障碍的关键因素 《医宗必读》指出:“按积之成也,正气不足,而后邪气踞之”,提示肝癌的核心病机在于人体之气。气作为生命活动的根本动力,具有推动、温煦、防御和固摄等生理功能,这与线粒体作为细胞能量转换器,参与调控细胞增殖、分化和凋亡等功能相契合。线粒体作为“细胞动力站”,不

仅通过代谢脂质和糖类产生ATP为细胞供能,还参与包括铁代谢、钙储存稳态、细胞增殖和信号转导等在内的多种重要细胞活动,在肝癌等疾病的发生发展中发挥重要的作用。这与正气充足时气血调和、脏腑功能正常运转,从而发挥气的推动、温煦等作用相似。气与线粒体功能可能存在一致性,气足则可抵御邪气侵袭,保障精微物质的生成与代谢,从而维持人体内环境稳定;而正气亏虚则气血生化不足,卫外不固,可能导致生物合成障碍,表现为ATP生成减少、线粒体复合物I活性显著降低和mtDNA拷贝数减少,从而加剧细胞缺氧和营养物质供应不足。细胞缺氧会进一步抑制线粒体的氧化磷酸化过程并促使线粒体产生大量ROS,引发氧化应激,损伤线粒体,并干扰机体内氨基酸、脂类、核苷酸和血红素的合成以及物质信息交换,导致受损线粒体、自由基和炎性物质大量堆积^[14-16]。此时气血生化乏源,运化失调,湿热、瘀血和痰浊等病理产物积聚于肝,与癌毒结合形成肝癌。

因此,“虚气”是肝癌发病之本,其与线粒体生物合成功能障碍可能存在一致性,共同影响肝癌的发生发展。

3.2 “留滞”是线粒体功能障碍的病理产物 随着病程迁延,气血阴阳渐亏,痰、瘀和毒等有形实邪留滞,形成“虚气”与“留滞”相互交织的病理状态,并伴随线粒体质量控制障碍及DNA异常。《寿世保元》云:“盖气者,血之帅也,气行则血行,气止则血止。”强调气的生化、布达失调,会影响津血的生成和运行,津血之变乃生痰瘀,而痰瘀互结又进一步阻滞气机。在肝癌中,人体内环境依赖于线粒体质量控制,其异常主要表现为动力学失衡、生物发生紊乱及自噬失调。线粒体动力学的失衡以及肝脏脂质和ROS积累可能互为因果,形成恶性循环,加剧肝损伤;线粒体生物发生异常可能导致代谢重编程及ROS生成增多,引发DNA损伤和细胞凋亡,促进肝癌的发生和发展;过度的线粒体自噬可导致ATP缺乏和细胞内钙过载,进而促进丝状肌动蛋白的降解以及基于板状足的迁移和肝癌细胞的侵袭^[17]。简言之,肝癌中线粒体质量控制异常可导致ATP生成不足,破坏线粒体稳态和钙稳态,造成受损线粒体堆积及ROS、脂质等生成增多,从而驱动肝癌进展。此过程或许与中医“肝气不足,痰瘀互结”的病机具有相似性:在肝癌中,正气渐衰,脏腑失和,津血输布异常,则痰瘀互结。痰性黏滞,易于留滞于体内,阻碍气血运行;瘀则阻塞脉络。痰瘀互结不仅阻碍气血运行,还会导致肝络损伤,使肝癌进一步恶化。

因此,“虚气”可致气滞,痰瘀“留滞”于体内,与线粒体功能障碍互相影响,共同作用于肝癌。

《内经》载:“邪之所凑,其气必虚。”若人体气虚日久,无力驱邪,则易受暴戾癌毒侵袭,癌毒依附痰瘀可加速肝癌进展。癌毒耗伤正气,正虚又促使邪毒积聚,形成恶性循环,加速病情恶化。在该阶段,癌毒占据主导,导致“免疫逃逸”,肿瘤广泛转移,mtDNA突变和拷贝数变异是肝癌进展中的常见事件。癌毒蓄积的生物学本质涉及线粒体凋亡通路异常,线粒体功能障碍导致的ATP匮乏迫使细胞启动自噬-凋亡失衡程序,同时线粒体源性ROS通过核因子 κ B通路激活炎性小体,促使白细胞介素-1 β 等炎性因子暴发。这种代谢-免疫双重紊乱不仅促进肿瘤相关巨噬细胞向M2型极化,更通过程序性死亡受体1及其配体轴诱导T细胞耗竭,形成“毒瘀胶着-免疫逃逸”的肿瘤微环境^[18]。临床研究显示,存在线粒体缺陷的肝癌患者其5年生存率显著降低^[19],这可能与中医“癌毒鸱张,阴阳离决”的病机演变高度吻合。随着肝癌进展,毒邪不断蓄积和演变,晚期肝癌患者常呈现气血两虚、脏腑功能衰竭之象,此时毒邪已深入脏腑,治疗难度显著增加。由此可见,“虚气”可致痰瘀发展,毒邪结聚,癌毒“留滞”于体内。

4 基于“虚气留滞”理论论治肝癌

4.1 扶正培本 《黄帝内经》确立的“虚则补之”治则,深刻阐释了扶正培本策略在肿瘤防治中的核心地位。该治法以补益气血、调和阴阳、充养脏腑为根本要义,通过固护机体正气、增强抗病能力以改善整体状态,进而实现抗癌目标,其应用贯穿肝癌治疗全程。临床实践表明,人参、黄芪等补益类单味药材,可通过增强线粒体生物合成功能来抑制肿瘤进展;其活性成分(如人参皂苷Rg3、黄芪甲苷)还可影响B淋巴细胞瘤-2(B-cell lymphoma 2, Bcl-2)家族蛋白的表达平衡,激活胱天蛋白酶(Caspase)-3/9级联反应,最终通过调控细胞周期进程诱导肝癌细胞凋亡^[20-22]。扶正清解方和四逆散等复方可益气扶正,通过显著降低线粒体膜电位,增强Caspase-3/9酶活性,特异性激活线粒体依赖性凋亡通路;参麦注射液则通过升高细胞内ROS水平引发DNA损伤,同时促进线粒体依赖性凋亡途径,显著抑制Hep3B细胞增殖^[23-25]。

4.2 行气通滞 中医防治肝癌秉承“通则不痛”的核心治则,主张通过行气活血、化痰散结之法重建气血输布,清除病理产物。在肝癌进展至“痰瘀互结”阶段时,治疗

需在扶正基础上强化行气通滞-化痰消瘀的综合干预。临床常联用木香、香附等理气通滞药物,配伍川芎、浙贝母等化痰散瘀之品,形成理气活血协同效应,这些药物可通过双重机制诱导肝癌细胞凋亡,校正氧化应激,调节线粒体质量控制失衡^[26-28]。健脾活血祛湿方和贝参茱萸方等组方依托益气健脾、疏肝理气和化痰散瘀的多靶点作用,可调节线粒体膜电位稳态,干预Bcl-2蛋白及其相关X蛋白表达比例,特异性激活线粒体凋亡通路,从而显著抑制肝癌细胞增殖^[29-30]。值得注意的是,艾迪注射液作为经典中成药,可通过抑制磷脂酰肌醇3-激酶/蛋白激酶B信号通路削弱细胞抗凋亡能力,激活丝裂原激活的蛋白激酶应激信号通路,协同诱导线粒体膜电位崩溃并激活Caspase-3/9凋亡执行蛋白^[31]。临床数据显示,该制剂可使肝癌细胞凋亡率提升2~3倍,同时显著降低肿瘤标志物甲胎蛋白的表达水平,其作为辅助治疗可有效提高患者生存率和客观缓解率^[32-33]。

4.3 解毒通络 肝癌日久化热成毒,形成“癌毒”病理产物,而正气持续耗损致正虚邪恋。对此,中医治疗主张在扶正基础上配合解毒通络法。例如,雷公藤、鸦胆子等清热解毒中药可上调Bcl-2相关X蛋白和Caspase表达,同时抑制Bcl-2蛋白的表达,从而激活线粒体凋亡通路抑制肝癌进展^[34-35]。解毒消癥饮可清热解毒、活血散结,对肝癌具有诱导癌细胞凋亡、抑制肿瘤生长和增强免疫功能等作用,其通过破坏线粒体跨膜电位稳态和诱导细胞内Ca²⁺浓度升高及ROS蓄积,触发凋亡级联反应,其作用机制涉及能量代谢障碍和氧化应激通路的调控^[36-37]。此外,华蟾素注射液、白花蛇舌草注射剂作为清热解毒、消瘀散结的经典中成药,可激活以线粒体为核心介导的内源性细胞凋亡途径,从而抑制肝癌细胞的增殖并诱导其凋亡,延长患者生存期,二者联用可产生协同效应,降低化疗药物所致的心脏毒性等副作用,体现“攻邪不伤正”的治疗特点^[38-40]。

5 小结与展望

本文通过整合“虚气留滞”理论与线粒体生物学,揭示了肝癌“正虚-邪滞-线粒体损伤”的病理轴心,构建了以“扶正培本、行气通滞、解毒通络”为核心的中西医协同治疗框架。本研究认为,肝癌以虚为本,气滞在先,痰湿为渐,瘀血为著,毒邪结聚,而成积证,肿瘤的转移也以“痰瘀互结”的形式流注于五脏六腑之间,可归纳为“虚气留滞”。故其治疗应遵循“补虚以培本、行滞以祛邪”的原则,以“扶正培本”“理气通滞”和“解毒通络”为

法,予以辨证论治。线粒体功能障碍在肝癌的病理过程中扮演重要的角色,其与“虚气留滞”理论存在密切的内在联系。基于“虚气留滞”理论,传统中医药可以通过调控线粒体膜电位、激活内质网应激和诱导 Caspase 级联反应等多靶点机制干预肝癌发生发展,充分发挥中医药“整体调控”的优势,以期为肝癌患者治疗方案的研究开辟新途径,从而提高患者的生存质量并改善预后。

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