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·专家论坛·

烟酸及其衍生物：从传统营养素到肿瘤防治的新认识

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[摘 要] 烟酸属于B族维生素，是人体必需的维生素之一。过去对烟酸功能的认知主要停留在营养素层面，如参与维持神经功能、促进代谢和发育、保护心脑血管等。随着研究的不断深入，近年来已有多项研究表明，烟酸及其衍生物能起到预防和辅助治疗癌症的作用。烟酸及其衍生物不仅影响肿瘤细胞的生物学功能、参与免疫调节，还能对烟酰胺磷酸核糖转移酶（NAMPT）抑制剂的抗肿瘤疗效起到辅助作用，并以多聚ADP-核糖聚合酶（PARP）依赖方式通过多种分子途径维持基因组的稳定性。本文总结了烟酸及其衍生物在肿瘤中作用的研究脉络和最新进展，并展望其进一步研究和应用方向，对烟酸及其衍生物在肿瘤综合防治中的应用有一定的指导作用。

[关键词] 烟酸；烟酰胺；肿瘤；烟酰胺腺嘌呤二核苷酸；烟酰胺磷酸核糖转移酶；免疫；基因组稳定性
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Renewed understanding of nicotinic acid and its derivatives: from traditional nutrients to cancer prevention and treatment

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[Abstract] Nicotinic acid belongs to B vitamins and is one of the essential vitamins for humans. In the past, the main cognition of nicotinic acid remained on its nutritional functions, such as participating in the maintenance of neural function, the promotion of metabolism and development, and the protection of cardio cerebral vessels. With the development of researches, in recent years, multiple studies have shown that nicotinic acid and its derivatives play key roles in the prevention and treatment of cancer. Nicotinic acid and its derivatives could affect the biological functions of tumor cells, participate in immune regulation, promote the antitumor efficacy of nicotinamide phosphoribosyltransferase (NAMPT) inhibitors, and maintain the genomic stability through a variety of molecular pathways in a poly ADP-ribose polymerase (PARP)-dependent manner. This review summarizes the research approaches and the latest progress in the studies of the role nicotinic acid and its derivatives play in cancer prevention and treatment and assess the prospects of its further research and application direction, with the hope of helping promote the application of nicotinic acid and its derivatives in comprehensive cancer prevention and treatment.

[Key words] nicotinic acid; nicotinamide (NAM); tumor; nicotinamide adenine dinucleotide (NAD); nicotinamide phosphoribosyltransferase (NAMPT); immune; genomic stability

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烟酸属于维生素B族,也称维生素PP或维生素B3,是人体必需的13种维生素之一。烟酰胺(nicotinamide,NAM)是烟酸的酰胺形式,可以和烟酸转化为单核苷酸化合物;NAM在氧化还原反应和DNA修复中不可或缺,它不仅直接影响正常细胞的生理能量代谢过程,而且在脂质代谢中也发挥关键作用,是脂肪酸合成所必需的辅酶[1]。此外,烟酸还是辅酶Ⅰ和辅酶Ⅱ,即烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide,NAD)和烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate,NADP)的前体物质,NAD作为一种辅酶可在脱氢酶反应中产生ATP,高浓度NAD能够通过抑制活性氧的产生来提升线粒体的功能,还参与维持基因组的稳定性和表观遗传调控,并参与调节细胞生存和死亡相关的多种途径[2]。最新研究[3]发现,烟酸具有对抗新冠病毒有效的药理靶点,不仅如此,越来越多的研究显示烟酸及其衍生物在皮肤癌[4]、结直肠癌[5]、乳腺癌[6]等肿瘤的预防与治疗中也具重要作用。本文以烟酸及其衍生物在肿瘤防治中的作用为切入点,围绕其对肿瘤细胞的生物学功能影响、免疫调节、对烟酰胺磷酸核糖转移酶(nicotinamide phosphoribosyltransferase,NAMPT)抑制剂的辅助作用和维持基因组稳定等四个方面进行阐述,系统地总结烟酸及其衍生物的抗癌机制(图1),并分析其未来发展方向。

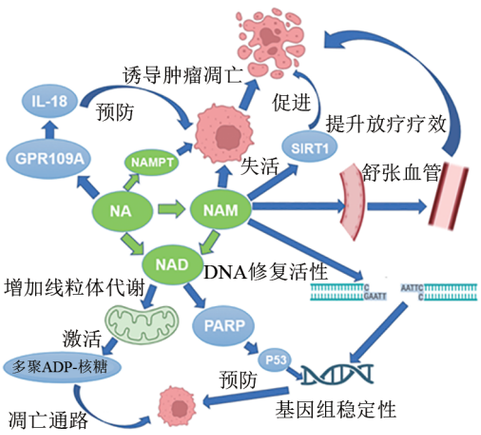

图1 烟酸及其衍生物预防与治疗肿瘤的机制

1 烟酸及其衍生物在肿瘤防治中的作用

1.1 预防和抑制皮肤癌的复发

人体内烟酸的缺乏会使NAM的合成减少,导致皮肤细胞对紫外线敏感性增加,并影响DNA修复反应,使皮肤癌的发病率升高。研究[7]发现,NAM可以增强DNA的修复活性,协助维持基因组的稳定性,对抗紫外线的免疫抑制作用。因此,通过补充烟酸可以起到预防皮肤癌、降低其发生率的作用。如紫外线照射会使角质形成细胞中的ATP减少,而NAM可以对此起到抑制作用,预防由紫外线诱导的ATP耗竭,还能增强细胞能量代谢相关酶的表达,从而降低小鼠的皮肤癌发病率,并且抑制皮肤癌的复发[4, 8]。临床试验结果[9]也显示,口服NAM是一种安全、耐受性好且经济有效的化学预防方法,可用于高危免疫耐受个体的基底细胞癌和皮肤鳞状细胞癌的预防。

1.2 改善化疗不良反应

在肿瘤患者的化疗过程中,常伴有造血系统损害,可能导致急性骨髓抑制和白血病等不良反应。大鼠模型中,烟酸缺乏会使DNA切除修复延迟,从而使有白血病潜力的细胞存活;通过补充烟酸,可增加大鼠骨髓多聚核糖的形成,显著降低大鼠模型中白血病的发病率[10]。临床上,大多数体重减轻的癌症患者都有烟酸缺乏的情况[11]。肿瘤患者可以通过摄入烟酸来补充NAD进而增强线粒体代谢,通过激活多聚ADP-核糖依赖的细胞凋亡通路来提高对肿瘤细胞的杀伤力,降低化疗不良反应的严重程度并改善烟酸缺乏的相关并发症[12]。

1.3 通过提升氧合改善放化疗效果

肿瘤组织中氧张力水平的降低会导致细胞缺氧,影响正常细胞与癌细胞的正常生理功能,但癌细胞会对缺氧会产生适应性,使其可以在缺氧环境中生存甚至增殖,从而有助于癌细胞的侵袭。放射治疗需要氧自由基破坏癌细胞,如果肿瘤的氧合不佳,缺氧区域内的癌细胞常会表现出对放疗的抗性;而大剂量的NAM可以抑制肌球蛋白轻链20磷酸化,使血管舒张、肿瘤内微血管流动增加,从而改善肿瘤的血流和氧合,提高放疗的杀伤力[13]。此外,碳离子和烟酰胺加速放疗(accelerated radiotherapy combined with carbogen breathing and nicotinamide,ARCON)同样是通过提高氧合与增加血流量来增强放疗效果。有研究发现,ARCON可以增强喉癌[14]、头颈癌[15]、膀胱癌[16]患者肿瘤局部的治疗作用;在接受放射治疗的膀胱癌患者中,ARCON显著提高了患者的OS和PFS[17]。在头颈癌患者Ⅱ期临床试验[18]中发现,ARCON治疗后肿瘤的局部控制率较高;Ⅲ期临床试验[19]中,ARCON可显著减轻患者放射治疗后贫血等不良反应。

2 烟酸及其衍生物在肿瘤发生发展中的作用及其机制

烟酸及其衍生物的抗癌作用体现在多方面,不仅可以直接或通过NAD-依赖性去乙酰化酶sirtuin-1

(SIRT1)等途径诱导肿瘤细胞凋亡,激活免疫系统预防肿瘤,还在维持基因组稳定方面起着重要的作用,并可以辅佐肿瘤抑制剂发挥作用。

2.1　NAM可通过抑制SIRT1调控肿瘤细胞的生物学功能

NAM是SIRT1的抑制剂,而SIRT1的失活是NAM诱导肿瘤细胞凋亡的机制之一[20]。黑色素瘤具有高度转移性,其转移受到SIRT1调控,而NAM可以引起SIRT1的失活,从而抑制C57BL/6小鼠腹部的B16-F10黑色素瘤细胞转移,提高小鼠生存率[21]。胰腺癌中,NAM抑制SIRT1、诱导癌细胞凋亡、G2/M期阻滞,并且降低癌细胞的侵袭能力[22-23];慢性淋巴细胞白血病中,NAM也起到抑制SIRT1的作用,并能够促进白血病细胞凋亡[24]。

此外,小鼠乳腺癌模型中,NAM可以使肿瘤体积减小[20]。有研究[25]发现,NAM可诱导乳腺癌MCF-7细胞发生凋亡。在体外实验中,NAM可以显著抑制肝内胆管癌细胞的增殖和迁移活力并且诱导其凋亡,同时抑制其EMT进程[26]。UTSAV等[27]发现,高剂量的烟酸与维生素C对结直肠癌HT-29、HCT-15细胞具有杀伤作用。

2.2　烟酸/GPR109A途径调节机体免疫

GPR109A是烟酸的受体,虽然烟酸是人体血液中的正常成分,但在生理条件下烟酸的浓度不足以激活GPR109A;在250 nmol/L浓度下,烟酸可激活其受体并产生效应[28-29]。Treg细胞在维持机体免疫平衡、预防自身免疫疾病和移植排斥方面发挥重大作用[30]。DC和巨噬细胞通过烟酸/GPR109A信号通路促进这两种细胞表达IL-10和Aldh1a等抗炎分子,还可促使幼稚T细胞分化为Treg细胞。GPR109A被激活后,还能使Treg细胞产生$CD4^+$ T细胞的频率与数量增加[31]。小鼠模型中,结肠上皮细胞内IL-18的表达呈GPR109A依赖性,IL-18表达增加可以抵御结肠炎症、降低结肠癌发生率[32]。

2.3　烟酸对抗肿瘤药物NAMPT抑制剂具有辅助作用

NAD在体内能量代谢、氧化还原反应及基因表达调控中必不可少,NAMPT是NAM合成NAD途径中的关键酶,抑制NAMPT会导致NAD减少;许多肿瘤细胞中,由于NAD的生物合成途径缺乏,使其更依赖于调控NAMPT途径进行NAD再生。与正常细胞相比,NAMPT在肿瘤细胞中过表达,导致肿瘤的侵袭性增加,影响患者预后,因此NAMPT是一个关键的抗肿瘤靶点[33]。目前,已有多种人工合成的小分子NAMPT抑制剂在体内、外实验中显示出极强的抗肿瘤活性,这些抑制剂以时间依赖方式抑制NAD的产生,NAD水平的持续降低会导致ATP缺乏最终使肿瘤细胞死亡。多种小分子NAMPT抑制剂的作用已在结直肠癌[34]、胰腺癌[35]、卵巢癌[36]等肿瘤模型中得到验证,但这些抑制剂的不良反应如视网膜毒性与血液学毒性阻碍了它们的应用。OLESEN等[37]将小分子抑制剂APO866与烟酸共同给药,发现小鼠模型中血小板减少的情况得到显著改善;GREEN等[38]对实验犬使用小分子抑制剂与烟酸联合用药,发现其视网膜和血液学毒性明显降低。将烟酸与NAMPT抑制剂合用可作为一种策略,以减轻NAMPT抑制剂的脱靶毒性,改善肿瘤治疗效果。

2.4　烟酸在维持基因组稳定性的作用

肿瘤的发生与细胞基因组的DNA序列改变密切相关,烟酸可以通过多种途径维持基因组的稳定性,这对癌症的预防十分重要。在临床试验中已证明补充烟酸可以减少DNA损伤,人体基因组的不稳定性与饮食中烟酸的摄入量呈显著的负相关[39]。在大鼠模型中,持续的烟酸缺乏会导致染色体不稳定性增加,当饮食中烟酸水平改变之后,骨髓首先作出响应[40]。

NAD^+是各种多聚ADP-核糖聚合酶(poly ADP-ribose polymerase,PARP)的底物,PARP-1可以与断裂的DNA链结合并被特异性激活[41];在被激活后,PARP-1在一些与DNA代谢和染色质结构相关的受体蛋白上合成多聚ADP-核糖,在DNA链断裂处,多聚ADP-核糖可以吸引与修复位点相关的其他蛋白[42];故而细胞中的NAD^+浓度会以PARP依赖方式通过多种分子途径影响基因组的稳定性。烟酸的摄入会导致NAD^+的浓度变化从而影响PARP-1活性,通过多聚ADP-核糖反应在DNA修复、重组和维持基因组稳定性中发挥作用[43]。由于大部分多聚ADP-核糖是由PARP-1所合成,因此烟酸的缺乏会导致PARP活性受损害,使其产物的表达和功能发生改变,而这些基因产物在细胞对基因毒性应激的反应中起着不可或缺的作用。与PARP-1具有极高同源性的PARP-2、PARP-3也可能直接受到烟酸和NAD^+的影响,现有研究[44]已经证明PARP-1和PARP-2的丢失会破坏DNA修复和表观遗传等重要的生物过程。

p53蛋白在协调DNA修复、维持基因组稳定和抑制肿瘤血管生成中起关键作用,p53被一些NAD^+依赖的过程所调控,是通过PARP-1激活的多聚ADP-核糖的共价受体;p53也有一个高亲和力的结合位点,可以与多聚ADP-核糖进行非共价相互作用,并被组蛋白去乙酰化酶去乙酰化[45-46]。当DNA损伤之后,PARP-1对DNA损伤的反应发生在几秒到几分钟内,而p53在几分钟到几小时内才会增加激活与表达,这表明多聚ADP-核糖基可能在基因毒性应激后作用于p53的上游,调节p53的表达和功能[4,48]。此外,在细胞凋亡的早期阶段,多聚ADP核糖可对p53进行翻译

后修饰,而在烟酸缺乏的细胞中,NAD^+的代谢变化使得p53表达改变[49-50]。多种癌症中都存在p53发生突变或表达下调的情况,p53的功能破坏后会导致调控细胞周期阻滞、凋亡的信号通路受损。

3 结 语

肿瘤防治一直是医学科研创新的重要领域,新的抗癌药物和技术不断涌现。烟酸属于普通的B族维生素,价格低廉且容易获得,随着越来越多的研究证明烟酸及其衍生物能对多种癌症起到预防和辅助治疗的作用,刷新了人们对这一常见维生素的认知。烟酸及其衍生物广泛地影响着肿瘤细胞的生物学功能、参与免疫调节、辅佐NAMPT抑制剂的作用,并参与基因组稳定的维持,而且作为肿瘤防治药物具有耐受性良好、性价比高的优势。在当前技术变革和抗癌策略更迭的形势下,如何使烟酸及其衍生物充分发挥其作用,应用到肿瘤综合防治策略制定中去,值得进一步探索和期待。

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