组氨酸三聚体核苷结合蛋白1和2与疾病相关的研究进展

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摘要 组氨酸三聚体核苷结合蛋白(HINT)属于HIT蛋白超家族, *HINT1*和*HINT2*基因分别位于人类染色体5q31.2和9p11区域, 编码产物分别是含126和163个氨基酸的蛋白, 相对分子质量分别约14 kDa和17 kDa, 二者之间有61%的序列同源性。HINT1在细胞中定位于细胞质和细胞核, HINT2定位于线粒体, 二者在组织中分布广泛。HINT1和HINT2两个亚型均为肿瘤抑制因子, 参与细胞增殖和凋亡, HINT1可通过调节Wnt/β-catenin信号通路以及$p27^{KIP1}$、AP1、TFIIH、MITF等转录因子的活性抑制肿瘤, HINT2可通过线粒体自噬和线粒体凋亡途径抑制肿瘤。该文就HINT1和HINT2的发现、分布、结构、酶活性、肿瘤作用机制及其与其他疾病的关系进行了系统综述并进行展望。为进一步揭示HINT1和HINT2在不同类型肿瘤中的分子抑制机制以及靶向治疗和药物研发奠定了理论基础。

关键词 组氨酸三聚体核苷结合蛋白; HINT1; HINT2; 肿瘤; 增殖和凋亡

Research Progress of Histidine Triad Nucleotide-Binding Protein 1 and 2 in Relation to Diseases

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Abstract HINT (histidine triad nucleoside-binding protein) belongs to the HIT protein superfamily. *HINT1* and *HINT2* genes are located in the 5q31.2 and 9p11 regions of human chromosome, respectively. The encoded products are proteins containing 126 and 163 amino acids, respectively. Their relative molecular masses are about 14 kDa and 17 kDa, respectively, and there is 61% sequence homology between HINT1 and HINT2. HINT1 is located in the cytoplasm and nucleus, and HINT2 is located in the mitochondria, both of which are widely distributed in tissues. The subtypes of HINT1 and HINT2 are tumor suppressor factors, which are involved in cell proliferation and apoptosis. HINT1 can suppress tumors by regulating Wnt/β-catenin signaling pathway, the activity of $p27^{KIP1}$, AP1, TFIIH, MITF and other transcription factors. HINT2 can suppress tumors by mitochondrial autophagy and mitochondrial pathways of apoptosis. This article reviews the discovery, distribution, structure, enzyme activity, tumor mechanism and other related disease of HINT1 and HINT2. It lays a theoretical foundation for further revealing the molecular inhibitory

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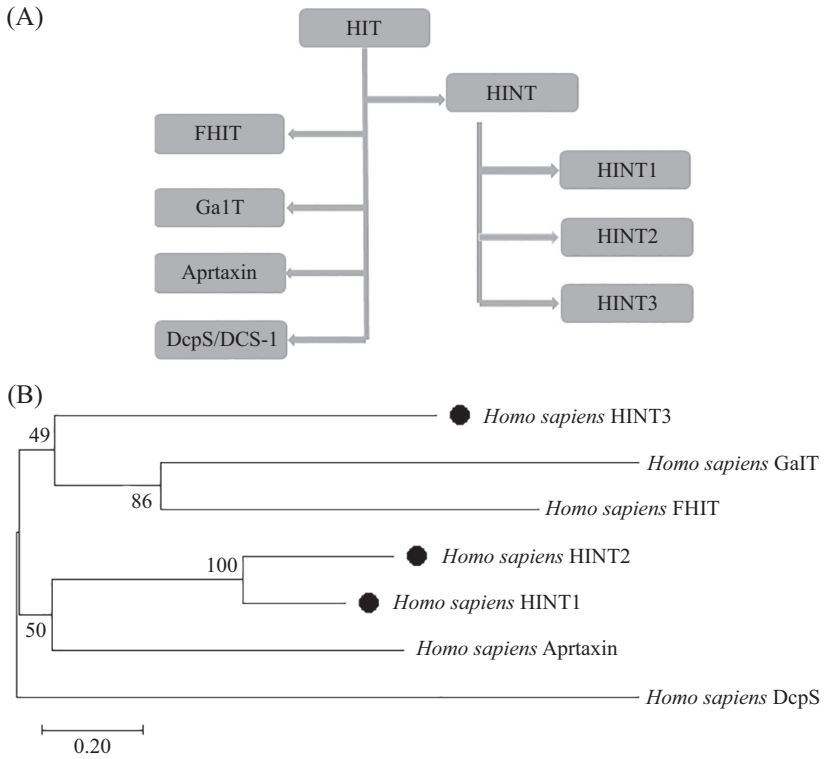
mechanism of HINT1 and HINT2 in different types of tumors, as well as targeted therapy and drug development.

Keywords histidine triad nucleotide-binding protein; HINT1; HINT2; tumor; proliferation and apoptosis

组氨酸三聚体(histidine triad, HIT)是一个具有核苷酸水解酶和转移酶活性的蛋白超家族, 因含有高度保守的活性位点基序HxHxHxx而被人知晓, 其中H为组氨酸, x为疏水性氨基酸[1-2]。HIT蛋白超家族成员包括组氨酸三聚体核苷结合蛋白(histidine triad nucleotide-binding protein, HINT)、脆性三联组氨酸(fragile histidine triad, FHIT)、1-磷酸半乳糖尿苷酸转移酶(galactose-1-phosphate uridyltransferase, GalT)、失用症蛋白Aprtaxin和清道夫脱帽酶(decapping scavenger, DcpS)[3-6](图1A), 其中HINT亚家族最为原始, 为HIT蛋白超家族中其他亚家族成员的祖先[2]。人类基因组中包括三个HINT亚家族成员基因, 分别为*HINT1*、*HINT2*和*HINT3*[7]。研究表明, HINT1和HINT2均为重要的肿瘤抑制因子, 与多种肿瘤的发生和发展密切相关。目前, HINT3相关研究较少, 不确定其是否为肿瘤抑制因子, 在HIT蛋白超家族的进化树中, HINT3与HINT1和HINT2不在同一个小分支(图1B), 有文献表明, HINT3是HIT蛋白超家族的独特分枝[8]。所以本文针对HINT1和HINT2的发现、分布、结构、酶活性、肿瘤抑制分子机制及其与其他疾病的关系进行综述。

1 HINT的发现

1985年, MCDONALD和WALSH[9]在牛脑中分离出HINT1, 且该团队于1990年对其进行鉴定和分析, HINT1最初被定义为蛋白激酶C抑制剂1(protein kinase C inhibitor-1, PKCI-1)[11-13], 但此活性没有得到进一步证实。KLEIN等[14]在酵母双杂交筛选系统中发现, HINT1能与PKCβ结合, 被鉴定为蛋白激酶C交互作用蛋白1(protein kinase interacting protein-1, PKCI-1)。随后, 该蛋白被鉴定为腺苷结合蛋白且含有组氨酸三聚体, 最终被命名为HINT1。HINT2曾



A: HIT蛋白超家族成员; B: HIT蛋白超家族进化树。

A: the members of HIT protein superfamily; B: the evolutionary tree of HIT protein superfamily.

图1 HIT蛋白超家族成员及进化树

Fig.1 The members and evolutionary tree of HIT protein superfamily

在人的正常结肠和肝癌细胞中被克隆出。

2 HINT的分布

*HINT1*和*HINT2*基因分别位于人类染色体5q31.2和9p11, 编码产物分别是含126和163个氨基酸的蛋白, 相对分子质量分别约14 kDa和17 kDa[15-16]。*HINT1*和*HINT2*基因之间有61%的同源性[17], 与HINT1相比, HINT2的N-端有35个氨基酸延伸, 对应于预测的线粒体输入信号[18]。HINT1在细胞中定位于细胞质和细胞核, HINT2定位于线粒体。HINT1广泛表达于人和其他哺乳动物的组织中, 在脑和脊髓中表达量最高[19-21]。HINT2在人的肝脏、肺、脑、肾脏等多种组织中都有表达, 其中在肝脏中表达量最高[18,22]。目前, 在动植物、真菌甚至在最小最简单的细胞支原体中都发现了HINT1蛋白的同源物[23-28], 而HINT2只在哺乳动物中被证实[11,29]。

3 HINT的结构

结构分析表明, HINT1是一个嘌呤核苷酸结合蛋白且是同源二聚体蛋白[30-31], 由α螺旋和β折叠构成, 在HINT1同源物的研究过程中发现, 其每个亚基包括两个α螺旋和五条β折叠, 其中α螺旋1(氨基酸18~24)和五条β折叠的一端结合, 而α螺旋2(氨基酸68~86)和折叠的另一端结合, 两个亚基形成一个同源二聚体[31]。HINT2也是一个同源二聚体蛋白且结构由a螺旋和β折叠构成。二者所具有的(α+β)类型的结构在同源二聚体结构的形成中发挥着重要作用, 是HINT同源二聚体结构保守的基础[11], 二聚体结构对于维持其酶活性是必需的[32]。如图2所示, HINT1和HINT2含有一个共同的保守结构域, 即PKCI_related。

4 HINT的酶活性

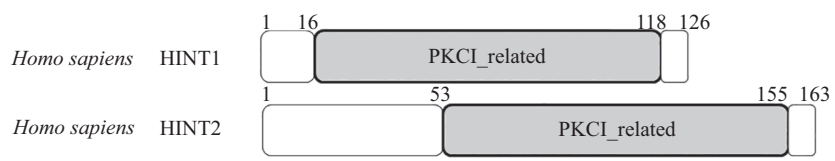
HINT具有核苷酸转移酶和水解酶活性[32]。BIEGANOWSKI等[33]利用液相色谱检测兔的HINT1对各种核苷酸的催化效率, 结果表明, 催化效率由高至低依次为AMPNH2>IDP、8-Br-ADP>GDP、ADP、IDP、AppA、NAD和NADH。HINT高度保守的活性位点基序HxHxHxx表现出催化活性, 第一个组氨酸不参与反应, 第二个组氨酸是高度保守的, 并参与第三个组氨酸的催化作用[17]。与HINT1相比, HINT2具有腺苷磷酸化酶活性[34]。HINT的反应底物不同, 催化效率不同, 不同物种的HINT对同一核苷酸的催化效率也会不同[35], 研究发现, HINT1的部分功能与其酶活性无关[2,36]。

5 HINT与肿瘤

研究表明, HINT1和HINT2都对肿瘤细胞有抑制作用。某些基因的表达水平发生改变, 如癌基因的激活或抑癌基因的失活, 使细胞具有无限增殖的能力, 最终导致肿瘤的发生[37-38]。

5.1 HINT1的肿瘤作用机制

研究发现, HINT1可抑制包括肝癌[39]、恶性黑素瘤[40]、非小细胞肺癌[41]和结肠癌[42]在内的多种人类肿瘤细胞的增殖。SU等[43]通过建立*HINT1*基因敲除小鼠模型发现, *HINT1*基因的缺失可以促进小鼠胚胎纤维原细胞(mouse embryonic fibroblast, MEF)的永生华, 增强小鼠对电离辐射的抵抗能力, 增强小鼠对肿瘤形成的敏感性, 表明HINT1可能具有肿瘤抑制作用。cDNA芯片技术及半定量RT-PCR的方法表明, *HINT1*在黑素瘤中低表达。基因克隆技术及构建*HINT1*重组真核表达载体, 转染并筛选出稳定转染且能高表达*HINT1*的单克隆人黑素瘤细胞A375, 这为后期研究*HINT1*基因在人黑素瘤中具体的作用机制建立了合适的细胞模型, 经研究发现, 高表达*HINT1*可抑制A375细胞的增殖并促进其凋亡[44]。*HINT1*能抑制人SGC7901胃癌细胞增殖且增强胃癌



HINT1和HINT2的保守结构域(PKCI_related)分别位于氨基酸(16~118)和氨基酸(53~155)。 HINT2与HINT1比对, N-端有37个氨基酸延伸, 对应于预测的线粒体输入信号。

The conserved domains (PKCI_related) of HINT1 and HINT2 are located at amino acid 16 to 118 and amino acid 53 to 155, respectively. Compared with HINT1, HINT2 has a 37-amino acid extension at the N-terminus, which corresponds to the predicted mitochondrial input signal.

图2 HINT1和HINT2保守结构域

Fig.2 Conservative domains of HINT1 and HINT2

细胞的放射敏感性[45]。腺病毒转染*HINT1*在143B和MG63细胞系中过表达可抑制细胞增殖、阻滞细胞周期并增加细胞凋亡[46]。HINT1主要的肿瘤抑制机制如下。

5.1.1 HINT1与DNA甲基化 目前的研究表明, 基因表达改变的机制主要有遗传学机制和表观遗传学机制。表观遗传学机制指核苷酸的序列不发生改变, 包括非编码RNA、染色体重构、组蛋白修饰以及DNA甲基化[47], 其中DNA甲基化是最主要的方式[48-49], 其在转录水平上影响基因的表达。DNA甲基化是一个可逆性的过程, 是肿瘤发生发展过程中的早期事件, 研究发现, HINT1在黑素瘤组织中低表达, 由于启动子区域高甲基化, 导致*HINT1*基因在转录过程中受阻, 进一步影响到HINT1蛋白的表达, 可能参与黑素瘤的发生发展, 这也是多种抑癌基因失活的重要机制[50]。

5.1.2 HINT1与Wnt信号通路 Wnt信号通路可参与调控细胞的增殖与凋亡过程[51], 该信号通路的异常与肿瘤的发生发展相关[52-53]。研究发现, Pontin(214~295)和Reptin(218~289)为HINT1的结合位点, HINT1可与二者直接结合, 构成β-连环蛋白(β-catenin)的配体[54], 在人的结肠癌细胞系SW480中抑制T细胞因子(T cell factor, TCF)-β-catenin介导的转录调控作用, 抑制一些相关基因, 如轴抑制蛋白2(axis inhibition protein, 2 *Axin2*)和细胞周期蛋白D1(*Cyclin D1*)[55]的转录, 从而抑制肿瘤细胞的增殖。

5.1.3 HINT1与凋亡相关基因 研究人员将*HINT1*基因过表达于人胚胎肾细胞HEK293、人肺癌细胞SW48及胸腺癌细胞MCF-7中, 检测凋亡相关基因的表达, 如促凋亡因子*Bax*基因和凋亡抑制因子*Bcl-2*基因的表达情况。研究结果表明, HINT1过表达能够通过上调Bax以及下调Bcl-2的表达水平诱导癌细胞的凋亡[36,56]。

5.1.4 HINT1与$p27^{KIP1}$ 研究表明, HINT1可调节细胞周期蛋白依赖性激酶抑制因子$p27^{KIP1}$的水平, 细胞周期调控机制紊乱与肿瘤发生密切相关, $p27^{KIP1}$蛋白在人体部分肿瘤中表达量降低, HINT1上调$p27^{KIP1}$的细胞水平的机制可能通过靶向SCF^{SKP2}泛素连接酶复合物来抑制其泛素化或通过抑制Src的表达来抑制Src对$p27^{KIP1}$的磷酸化, 因此, HINT1能够通过调节$p27^{KIP1}$的活性来抑制肿瘤细胞的增殖[57]。

5.1.5 HINT1与AP-1转染 编码SH3结构域蛋白(protein “plenty of SH3 domains”, POSH)的质粒DNA可以刺激c-Jun的磷酸化和活化蛋白-1(activator protein-1, AP-1)的活性, 与HINT1共转染反而抑制二者活性。免疫共沉淀研究表明, HINT1与POSH和c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)在体内形成复合物[42,58], HINT1通过与POSH-JNK2复合物结合抑制AP-1活性, 从而抑制c-Jun的磷酸化, 这一作用可能有助于HINT1的抑癌作用。

5.1.6 HINT1与其他转录因子 HINT1与细胞周期蛋白依赖性蛋白激酶7(cyclin-dependent protein kinase 7, Cdk7)相互作用, 从而调控基础转录因子TFIIH与其靶基因的结合[7,59]。HINT1能够抑制小眼畸形相关转录因子(microphthalmia inducing transcription factor, MITF)的转录活性, MITF在肥大细胞及黑素细胞等的生长发育中发挥十分重要的作用, HINT1能够抑制MITF的转录活性, 研究表明, HINT1可能与细胞的生长发育相关[60]。

5.2 HINT2的肿瘤作用机制

HINT2蛋白存在于线粒体, 线粒体是大多数真核细胞中都存在的、在细胞能量代谢过程中起关键作用的细胞器, 对于维持细胞正常的生命活动是十分重要的。研究显示, 与正常组织相比, 结肠癌中HINT2的表达量降低[61], 利用小干扰RNA技术下调结肠癌细胞HINT2的表达, 发现其侵袭及迁移的能力明显增强; HINT2在人乳腺癌细胞株MCF7中高表达能增强其对紫杉醇注射液的敏感性[62], 结果表明, HINT2可抑制肿瘤细胞的增殖。HINT2主要的肿瘤抑制机制如下。

5.2.1 HINT2与细胞自噬 自噬是参与膜、蛋白质、病原体以及细胞器运输和降解的细胞过程[63], 是在细胞应激条件下诱导的高度保守的分解代谢过程, 在能量或营养不足的情况下, 自噬可防止细胞损伤, 维持细胞生存, 还可以对细胞毒性损伤作出反应。因此, 自噬主要具有保护细胞的功能, 使其适应环境的不断变化[64], 这个基本的细胞过程在发育、可塑性以及对疾病和损伤的反应中至关重要[63]。通过双向电泳结合串联质谱分析发现, HINT2在饥饿处理引起自噬的细胞中表达量明显降低, 用自噬抑制剂3-MA处理过的细胞在相同条件下前后无差异, 由于HINT2蛋白定位于线粒体, 所以HINT2蛋白被认为是一种自噬相关的候选线粒体蛋白[65]。自噬在肿瘤发生过程中可以使肿瘤细胞失去生存的能力, 进而

抑制肿瘤的生长, 因此, HINT2可能通过自噬抑制肿瘤的生长。

5.2.2 HINT2与线粒体 成年小鼠心肌梗死后过表达HINT2可通过维持线粒体NAD的稳态保护其心脏功能[29]。研究发现, HINT2可通过线粒体凋亡途径促进肿瘤细胞凋亡, 抑制肿瘤细胞增殖, 并且可在肿瘤迁移过程中发挥重要作用[66-68]。肝癌细胞中的HINT2与正常肝细胞中的HINT2相比, 表达量较低, 高表达HINT2的肝癌细胞可促进Caspase介导的细胞凋亡, 从而抑制肝癌细胞的生长[69]。

6 HINT与免疫

有研究显示, 利用鲍血淋巴细胞全长cDNA文库筛选出了四个鲍免疫相关全长基因, 其中包括*HINT1*基因, 利用分子生物学、生物信息学分析等技术对鲍HINT1的结构进行研究, 经脂多糖(lipopolysaccharides, LPS)刺激后, 鲍HINT1表达量上升, 表明鲍HINT1与免疫功能相关[70]。在经过LPS刺激的高表达HINT2的HaCat细胞中, 发现促炎因子肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和白介素-6(interleukin-6, IL-6)低表达, 而抗炎因子IL-10高表达, 表明HINT2与免疫和炎症反应相关[71]。

7 HINT与其他疾病

除了与肿瘤密切相关外, HINT与精神分裂症、脑老化和肝纤维化等人类疾病也关系密切, 其中HINT1在这三种疾病中都有研究(图3)。

7.1 HINT1与精神分裂症

HINT1在中枢神经系统中高表达, 这揭示了其在精神疾病方面可能发挥重要作用[72]。研究发现, 精神分裂症患者的背外侧前额叶皮层HINT1低水平表达[73-75], 且*HINT1*基因位于与精神分裂症高度相关的基因位点(5q31.2)[76-77], 表明HINT1与精神分裂症有关, 精神分裂症是一种常见的精神疾病, HINT1与精神分裂症的关系可能仅出现于男性患者中[78-79]。精神分裂症的病因较为复杂, 包括表观遗传变化和遗传易感性与环境的相互作用[80]。研究发现, 精神分裂症发生的原因可能是缺乏HINT1进而导致突触后多巴胺传递异常[81], 也有研究发现, *HINT1*基因突变可导致精神分裂症。

7.2 HINT与脑老化

脑老化是许多神经性疾病如阿尔茨海默病(Alzheimer's disease, AD)的主要症状之一, 但脑老化的机制复杂, 目前仍不清楚。研究人员对倭狐猴颞叶皮层转录组进行分析, 发现年轻并且健康的动物的

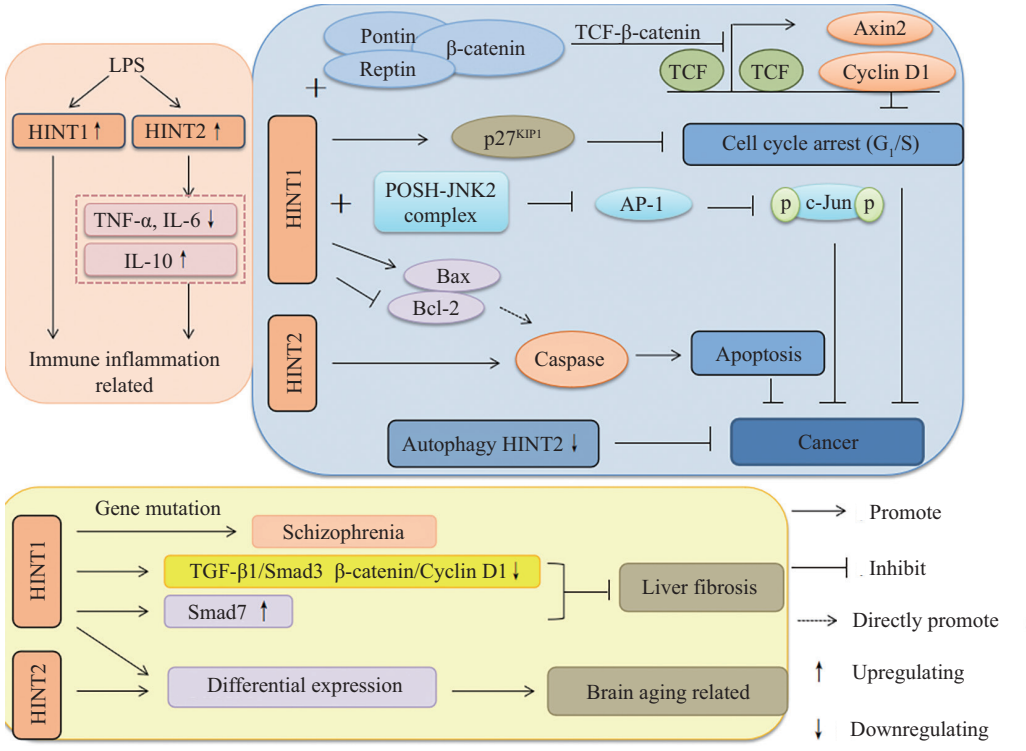


图3 肿瘤、免疫及其他疾病(与HINT1和HINT2相关)

Fig.3 Cancer, immune and other diseases (HINT1- and HINT2-related)

HINT1和HINT2与年老并且健康的动物的HINT1和HINT2表达存在差异[2,82], 这表明, HINT可能在脑老化的过程中发挥着重要作用。

7.3 HINT1与肝纤维化

研究发现, 过表达*HINT1*基因可以抑制肝纤维化, 其作用机制主要是通过减少肝内细胞外基质(extracellular matrix, ECM)的沉积并抑制肝星状细胞(hepatic stellate cell, HSC)的活化, 同时下调转化生长因子-β1(transforming growth factor-β1, TGF-β1)/Smad3和β-catenin/Cyclin D1的表达以及上调Smad7的表达而实现的, 这可能成为治疗肝纤维化的新的思路[83]。

8 展望

本文就HINT1和HINT2的发现、分布、结构、酶活性、对肿瘤的抑制机制及其与其他疾病的关系进行综述。HINT1和HINT2的表达与肿瘤细胞的增殖呈负相关, 它们均为肿瘤抑制因子, 在肿瘤细胞中的抑制机制为肿瘤的治疗及药物研发提供重要的理论依据, HINT1和HINT2的表达有望成为一种新的预后指标用于临床监测。HINT3蛋白是否如HINT1和HINT2蛋白一样, 同为肿瘤抑制因子, 还有待研究。哺乳动物的HINT同源基因几乎是相同的, 尽管与其他真核生物的序列同源性较低, 但其功能在进化上是保守的[33], 目前, 关于HINT1和HINT2蛋白功能的研究主要集中于人类, 而对于其他物种HINT1和HINT2的生物学功能及其作用机制研究较少, 我们团队已对原始脊椎动物七鳃鳗的HINT家族开展研究, 旨在为该家族蛋白的进化研究以及蛋白功能研究提供依据。此外, HINT1在神经性疾病及免疫和炎症发生中的具体机制尚不清楚, 相信随着研究的不断深入, 可阐明人类及其他物种中HINT1和HINT2的作用机制, 对疾病诊断和治疗具有潜在价值。

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