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PLEKHA蛋白家族在恶性肿瘤中的研究进展

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摘　要

PLEKHA是含有pleckstrin同源(PH)结构域的蛋白家族，PH结构域是约100个氨基酸的蛋白质模块，其存在于参与磷酸肌醇代谢、信号传导和细胞骨架组织的多种蛋白质中，PLEKHA蛋白家族包含三个独立的亚家族。而PLEKHA4/5/6/7与多种人类肿瘤关系密切，遂本文对PLEKHA蛋白家族与恶性肿瘤的关系做一综述，以明确PLEKHA蛋白家族在恶性肿瘤中的作用。

关键词

PLEKHA，蛋白家族，黑色素瘤，乳腺癌，结肠癌

Research Progress of PLEKHA Protein Family in Cancer

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Abstract

PLEKHA is a family of proteins containing the pleckstrin homologous (PH) domain. The PH domain is a protein module of about 100 amino acids that is present in a variety of proteins involved in phosphoinositol metabolism, signaling, and cytoskeletal organization. The PLEKHA protein family contains three separate subfamilies. PLEKHA4/5/6/7 is closely related to a variety of human tumors, so this paper reviews the relationship between PLEKHA protein family and malignant tumors to clarify the role of PLEKHA protein family in cancer.

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Keywords

PLEKHA, Protein Family, Melanoma, Breast Cancer, Colon Cancer

1. 引言

PLEKHA 是含有 pleckstrin 同源(PH)结构域的蛋白家族，该家族包括八个成员，即 PLEKHA1、PLEKHA2、PLEKHA3、PLEKHA4、PLEKHA5、PLEKHA6、PLEKHA7 和 PLEKHA8，这是由于它们都含有 pleckstrin 同源(PH)结构域[1]。PH 结构域是约 100 个氨基酸的蛋白质模块，其存在于参与磷酸肌醇代谢、信号传导和细胞骨架组织的多种蛋白质中[2]，有文献表明，PLEKHA 蛋白家族包含三个独立的亚家族，即 PLEKHA 4/5/6/7，PLEKHA 1/2 和 PLEKHA 3/8 [3]；这是由于它们的 PH 结构域具有不同的磷酸肌醇结合性质，并且功能上属于不同的 PH 结构域家族[1] [4]。据文献分析，PLEKHA4/5/6/7 与多种人类肿瘤关系密切，遂本文主要分析 PLEKHA4/5/6/7 在恶性肿瘤中的进展。PLEKHA4、PLEKHA5、PLEKHA6 和 PLEKHA7 潜在地与钙粘蛋白复合物相关[4] [5]，该蛋白家族在多种疾病中均有差异表达或突变，尤其在胶质瘤、黑色素瘤、乳腺癌、结直肠癌等恶性肿瘤中。因此，本文对 PLEKHA 蛋白家族在恶性肿瘤中的研究进展做一综述。

2. 胶质瘤

胶质瘤是中枢神经系统中最常见的侵袭性和致死性肿瘤，也是主要的脑原发性恶性肿瘤[6]。有研究表明，胶质瘤组织中 PLEKHA4 的表达明显高于癌旁正常组织，PLEKHA4 高表达的胶质瘤患者的总体生存期(OS)，无进展间隔期(PFI)和疾病特异性生存期(DSS)显著短于 PLEKHA4 低表达患者。PLEKHA4 是脑低级别胶质瘤一个独立的预后生物标志物，并与胶质瘤的免疫浸润相关，靶向 PLEKHA4 可能会改善胶质瘤的免疫治疗[7]。这些发现还需要基础实验和未来进一步的临床试验来证实。

3. 黑色素瘤

据报道，PLEKHA4 在黑色素瘤中表达较高，但在健康黑素细胞中表达水平较低[8]。黑色素瘤是皮肤癌中最具侵略性和致命最的形式，并且在过去几十年中全世界范围内显示出日益增长的发病率[9]。大多数黑色素瘤的根本原因是相对少量基因的体细胞突变[10]。调节增殖的 Wnt/β-连环蛋白信号传导在包括黑色素瘤在内的几种癌症中异常活跃[11]。PLEKHA4 可促进黑色素瘤细胞中 Wnt/β-连环蛋白信号传导，其信号传导的主要作用是通过促进 G-S 细胞周期的转换，从而促进黑色素瘤细胞的存活和增殖。且 PLEKHA4 是 BRAF 和 NRAS 突变型黑色素瘤中增殖表型的重要介体[12]。有实验表示，在裸鼠中敲除 PLEKHA4 可以抑制黑色素瘤的生长。这也就说明靶向 PLEKHA4 降低其水平，可减弱 Wnt/β-连环蛋白信号传导，并阻断通过 G1/S 细胞周期转变的进展，进一步抑制黑色素瘤细胞的增殖[12]。如果能以选择性靶向的方式最大限度地减少对非癌组织的损伤，抑制 Wnt 信号传导是一种有希望的新抗癌疗法[13]。

PLEKHA5 在脑发育中起作用，但其在人类癌症中的功能和精确作用机制尚未确定[14]。大多数黑色素瘤的患者在疾病过程中发生脑转移[15]；脑转移瘤具有高度侵袭性和迁移性[16] [17]。目前，5 年时间黑色素瘤患者发生中枢神经转移的累积风险约为 7% [18] [19]。具有脑转移的黑色素瘤患者的中位总生存期为 2.5~6 个月[20]。有文献表明，PLEKHA5 被描述为脑中远处黑色素瘤转移的介质[21]。多项证据表

明，黑色素瘤细胞粘附于脑内皮细胞，并通过破坏紧密连接蛋白和粘附连接蛋白以干扰脑内皮细胞的相互作用的方式促进转移，此外，蛋白水解酶对于转移性细胞穿过血脑屏障并占据脑的能力是重要的[22]。PLEKHA5 在患有早期黑色素瘤脑转移的患者的脑内肿瘤和脑外肿瘤中均上调[21]，这表明 PLEKHA5 允许黑色素瘤细胞有效地通过血脑屏障[23]。有实验表明，PLEKHA5 的敲低减少体外模型中亲脑细胞穿过血脑屏障的增殖和迁移[21]。PLEKHA5 通过与 PI3K/AK 信号通路的串扰，刺激细胞周期转换，介导肿瘤细胞生长[24]。有研究发现，PLEKHA5 主要定位于质膜，而膜相关的 PLEKHA5 在迁移过程中集中在细胞前缘的肌动蛋白聚合位点[25]。临床前体内和体外研究表明，PI3K 途径抑制剂可能是黑色素瘤脑转移的有效策略[26] [27]。靶向小分子抑制剂可能会改善黑色素瘤脑转移患者反应和总体存活。也有文献提出 PLEKHA5 参与了肝脾 T 细胞淋巴瘤的发病机制[28]，但其没有详尽的描述。

4. 胃癌

胃癌是一种复发率较高的恶性肿瘤，是世界范围内仅次于肺癌和肝癌的肿瘤相关死亡原因[29]。肿瘤微环境(TME)对肿瘤的发生发展起着重要作用，主要依赖于癌细胞、免疫系统和肿瘤微环境三者之间的相互作用[30] [31]。肿瘤相关巨噬细胞(TAMs)被认为是肿瘤微环境的关键因素，也是肿瘤侵袭性的促进因素。然而，TAMs 对胃癌进展作用的详细机制仍未确定。PLEKHA4 mRNA 和蛋白在胃癌来源的外泌体中丰富存在，且在与胃癌细胞外泌体共培养及体外诱导的 M2 型巨噬细胞中被激活，因此，推测胃癌外泌体中的 PLEKHA4 可能是调控肿瘤相关巨噬细胞 TAMs 表型极化的极为重要的目标分子，此外，PLEKHA4 在胃癌组织中的表达与胃癌患者的发病年龄、肿瘤局部浸润深度和病理分期均具有显著相关性，提示 PLEKHA4 是促进胃癌进展的关键分子。并且体外实验证明，在外泌体中敲低 PLEKHA4 可以抑制巨噬细胞向 M2 表型的极化[32]，抑制 PLEKHA4 的表达有望成为胃癌的潜在治疗策略。

弥漫型胃癌由低分化癌细胞组成，通常表现出侵袭性进展。弥漫性胃癌的特征是快速浸润性生长、大量基质纤维化和腹膜转移[33] [34]。这些侵袭性特征导致弥漫性胃癌患者预后不良[35] [36]。有文献表示，在弥漫性胃癌中观察到 MET 和 FGFR2 的基因扩增[37] [38]。而 MET 基因扩增与胃癌患者的不良预后相关[38] [39]。MET 信号传导调节恶性肿瘤的细胞迁移和侵袭、细胞增殖和存活以及血管生成[40]。有报道，PLEKHA5 在 MET 信号传导的下游被酪氨酸磷酸化，PLEKHA5 沉默显著阻断弥漫性胃癌的腹膜播散，这种抑制作用最可能是通过 PLEKHA5 沉默导致细胞迁移、侵袭和存活减少而实现的[41]。以 PLEKHA5 为靶点的分子靶向治疗 Met 依赖性肿瘤可能会是一个新的治疗方向。

5. 肺癌

肺癌是世界范围内发病率最高的肿瘤，在我国一直居于肿瘤发病率和死亡率的首位[42]。肺癌根据病理组织不同被分类为非小细胞肺癌和小细胞肺癌。小细胞肺癌是肺癌中比较少见的类型，起源于肺内神经嵴细胞，属于神经内分泌肿瘤，约占肺癌病例的 15%，相比于非小细胞肺癌，小细胞肺癌的分化程度低，生长速度快，更容易恶化，因此，小细胞肺癌的预后普遍较差，5 年生存率不足 7% [43]。有研究表明，PLEKHA5 在小细胞肺癌组织中高表达，高表达时患者的预后较差，且与远处转移有关。进一步分析发现 PLEKHA5 是脑转移的一个危险因素，且仅与脑转移相关，而与其他部位的转移无关，表明该指标可能是小细胞肺癌脑转移的一个特异指标[44]。PLEKHA5 的 PH 结构域可以与 PI3P 结合，提示 PLEKHA5 可以调节 PI3K 信号通路的活性。而 PI3K/Akt/mTOR 信号通路在小细胞肺癌中异常激活，PI3K 的激活能使 PIP3 增加，PIP3 进一步与 Akt 结合，磷酸化下游分子从而加速细胞周期和抑制肿瘤细胞凋亡，并与小细胞肺癌的耐药相关[45]。小细胞肺癌中 PLEKHA5 的具体分子机制，尤其是 PLEKHA5 是否能特异性地预测肿瘤脑转移，还有待进一步研究。有文献表示，PLEKHA6 在头颈癌中差异甲基化[46]，其高表达被证明是肺癌的良性预后因子[47]，但没有详细的文献描述。

6. 乳腺癌

许多实验研究表明，PLEKHA5 在肿瘤转移中起作用，并且发现 CRISPR-Cas9 介导的 PLEKHA5 敲除增强了体外细胞迁移和侵袭，体内原位移植试验表明，在多个细胞系中敲除 PLEKHA5 促进肿瘤细胞转移到其他远端器官，如肺和肝[48]，进而发现 PLEKHA5 的表达水平在有转移的乳腺肿瘤中显著低于无转移的乳腺肿瘤，这提示，PLEKHA5 在乳腺癌转移中作为肿瘤抑制剂，其中 PLEKHA5 敲除可促进肿瘤迁移和侵袭。这显然与先前研究的 PLEKHA5 在黑色素瘤中的肿瘤促进功能[21] [24]相矛盾。造成这种差异的确切原因目前尚不清楚；然而，一项先前的研究鉴定了两种形式的 PLEKHA5 mRNA，并发现长形式的 PLEKHA5 在脑中特异性表达，而短形式的 PLEKHA5 普遍表达[14]，这可能是造成这种差异出现的原因，但具体机制还需进一步研究。

乳腺癌根据其浸润特征分为浸润性和非浸润性，并且包括一系列肿瘤类型，其中导管癌是最常见的，小叶癌占总数的约 5%~10%。乳腺导管癌与小叶癌的形态学特征及浸润方式的不同有助于诊断。有文献表明，PLEKHA7 可将乳腺浸润性小叶癌与浸润性导管癌区分开来[49]。PLEKHA7 可以在正常乳腺导管和小叶的上皮连接处以及 G1 和 G2 导管癌内的管状和微乳头状结构处检测到。PLEKHA7 在 G3 导管癌中显著降低，在小叶癌中检测不到[50]。在小叶癌中未检测到 PLEKHA7 标记，可能是由于 PLEKHA 7 与其在粘附小带(ZA)处的结合配偶体，(例如 p120ctn) [51]和 afadin [52])的相互作用改变，而 afadin 和 p120ctn 能调节乳腺癌细胞的侵袭表型[53] [54]。例如 E-钙粘蛋白与特定 p120ctn 同种型的表达不平衡促进侵袭性播散和转移[55]。因此，PLEKHA7 与 p120ctn 相互作用，PLEKHA7 的缺失可能通过改变 p120ctn 的稳定性和信号输出而促进肿瘤侵袭性[56]。也有报告称，晚期乳腺癌和肾癌[57]以及炎性乳腺癌[58]中存在 PLEKHA7 的错误定位或丢失。在乳腺癌和肾癌中未发现 PLEKHA7 与肿瘤类型或级别之间的相关性[57]。有报道称，与低级别上皮性卵巢癌相比，PLEKHA7 在高级别中降低，且 PLEKHA7 高表达与改善患者预后相关[59]。也有文献表明，PLEKHA6 在乳腺癌组织中高表达时，乳腺癌患者的死亡率会降低[60]。

7. 结肠癌

结肠癌是第三个常见和第二个致命形式的癌症[61]。这意味着我们对疾病的理解仍有不足[62]。PLEKHA7 最为人所知的是作为调节细胞质粘附连接(AJs)蛋白质组装的支架，确保细胞间粘附和紧密连接屏障完整性[63] [64]。AJs 是一种细胞－细胞粘附复合物，由钙粘蛋白和连环蛋白家族蛋白组成，对于维持上皮完整性至关重要，其参与肿瘤发生和癌症进展[59] [65]。有文献说，AJs 完整性的破坏是上皮癌的标志[66] [67]。结肠肿瘤的一个共同特点是上皮组织架构完整性破坏和失去，这发生在癌症早期甚至癌前病变[68] [69]，然而，结肠上皮结构的破坏有助于促肿瘤发生细胞转化的程度仍不清楚[68] [69] [70]。有多个文献表明，E-钙粘蛋白在大多数检查的肿瘤中表达，并且 E-钙粘蛋白-p120 复合物是癌细胞存活、增殖、非贴壁依赖性生长以及集体细胞迁移所必需的[57] [70]。有文献表明，PLEKHA7，是一种基于 E-钙粘蛋白-p120 连环蛋白的连接相关的蛋白质，募集 RNA 干扰(RNAi)的核心组分，包括 AGO2、DROSHA 和 DGCR8，以使顶端 AJs 成熟，从而调节一组 miRNA 和 mRNA 的水平[57] [71]。PLEKHA7 和 RNAi 组分位于正常结肠组织中的顶端 AJs，但在肿瘤中的细胞－细胞接触区域不存在[72]。先前有研究表明，PLEKHA7 是将 RNAi 组分募集到粘附连接所必需的，PLEKHA7 耗尽会导致 RNAi 组分的连接定位的丧失，导顶端粘附小带的完整性破坏[57] [71]。PLEKHA7 和 RNAi 组分的连接定位的丧失导致 miRNA 的加工和活性降低，导致致癌基因上调，以及导致促肿瘤发生细胞转化[57] [71] [72]，也有文献表明，RNAi 的顶端连接定位在结肠肿瘤和低分化结肠癌细胞系中被破坏或丢失，这与粘附连接组分 PLEKHA7 的失调相关。实验表明，在侵袭性结肠癌细胞的粘附连接处恢复了 PLEKHA7 表达，从而恢复了 RNAi 组分

的连接定位，并在体外和体内抑制癌细胞生长[72]。这就鉴定了 PLEKHA7 在上皮 AJs 的局部有肿瘤抑制机制。然而，也有研究表明，抑制突变型 KRas 结肠癌细胞中的 PLEKHA7 会降低与细胞增殖、附着和迁移相关的 KRas 下游信号传导以及抑制肿瘤生长，但在野生型 KRas 结肠癌细胞中没有这种影响[73]。PLEKHA7PH 结构域可能是抑制所有形式的突变型 KRas 肿瘤有用的药物靶标，但需要更多的工作来开发具有更大选择性和优化的药代动力学性质的抑制剂。

8. 上皮性卵巢癌

在上皮性卵巢癌细胞中，E-钙粘蛋白在肿瘤进展期间显示出高水平的表达[74] [75]，其通常与 N-钙粘蛋白一起表达，除了其与化学抗性的关联之外，N-钙粘蛋白在这些肿瘤中的调节和激活信号传导的作用仍不清楚[76]。之前报道称，通过 E-钙粘蛋白形成细胞-细胞接触有助于上皮性卵巢癌细胞的增殖，其通过将 PI3K-p85 亚基募集到细胞膜上，从而导致 PI3K/AKT 活化[75]。在极化上皮中，E-钙粘蛋白的生长抑制作用取决于 PLEKHA7 的表达，PLEKHA7 是 ZA 的一种成分[57]。较高水平的 PLEKHA7 抑制 E-钙粘蛋白/EGFR 结合，从而负面影响上皮性卵巢癌细胞的生长和致瘤潜力，在高级别浆液性卵巢癌中观察到 PLEKHA7 表达显著降低[59]。PLEKHA7 表达与无进展生存期(PFS)和总生存期(OS)的相关性在两个公开可用的数据集中进行了分析[77] [78]，所述数据集分别包含来自 285 和 107 名上皮性卵巢癌患者的基因表达数据。在两个数据集中，较高的 PLEKHA7 表达与较长的无进展生存期(PFS)和总生存期(OS)显著相关[59]；最新的数据表明，PLEKHA7 在上皮性卵巢癌中丢失或离域，其表达可能与预后相关。低或缺乏 PLEKHA7 在上皮性卵巢癌的表达允许 E-钙粘蛋白与 EGFR 在细胞表面形成复合物，从而有助于促进生长的信号传导；在 PLEKHA7 过表达时，E-钙粘蛋白与 EGFR 的结合丧失，随后 EGFR 活化受到抑制，这与之前描述的高级别浆液性卵巢癌患者中 PLEKHA7 表达低的证据一致。PLEKHA7 高表达与上皮性卵巢癌的良好预后相关[59]。也有文献表明，PLEKHA7 在乳腺癌和肾癌中错误定位或丢失，并且通常与 E-钙粘蛋白丢失无关[50] [57]。临床上，PLEKHA7 有作为侵袭性较低的上皮性卵巢癌的可能标志物。

9. 结论

PLEKHA 是含有 pleckstrin 同源(PH)结构域的蛋白家族，主要参与磷酸肌醇代谢、信号传导和细胞骨架组织结构的完整。PLEKHA4 可促进肿瘤细胞中 Wnt/β-连环蛋白信号传导，从而促进肿瘤细胞的存活和增殖，其主要在黑色素瘤和胶质瘤中表达。PLEKHA5 已被鉴定为转移性黑素瘤和胃癌中的肿瘤生长调节因子。PLEKHA6 在头颈癌中差异甲基化，其高表达是肺癌和乳腺癌的良性预后因子。PLEKHA7 则是 PLEKHA 蛋白家族中研究最充分的，PLEKHA7 通过锚定到微管参与钙粘蛋白的连接和稳定紧密连接屏障功能、RNA 干扰机制(RNAi)和 RNA 诱导沉默复合物(RISC)的连接募集以调节信号传导和肿瘤生长，以及连接蛋白和跨膜蛋白复合物的连接募集，主要在晚期乳腺癌、肾癌、卵巢癌和结肠癌中被研究，并与其肿瘤细胞存活、增殖及迁移相关。总之，PLEKHA 蛋白家族在恶性肿瘤的发生发展中有重要作用，进一步的临床研究可能会为更多的患者提供新的治疗方向。

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