细胞膜结构脂质与膜流动性影响肿瘤侵袭转移的研究进展

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摘要: 恶性肿瘤癌变过程中细胞膜脂质构成发生显著变化, 并影响膜流动性和功能。细胞膜流动性涉及肿瘤侵袭转移的多个步骤, 包括细胞运动、黏附、膜分子横向扩散、信号传导、物质交换等活动。本文探讨了正常细胞和恶性肿瘤细胞的膜脂质构成和流动性差异, 以及与癌细胞侵袭转移潜力之间的相关性, 并指出通过改善细胞膜流动性或干扰膜脂质构成, 能够抑制肿瘤增殖、侵袭和转移, 这种思路更侧重于改变细胞膜的生物物理特性, 为预防和治疗癌症转移提供了一种新策略。

关键词: 细胞膜; 膜脂质; 脂筏; 膜流动性; 肿瘤转移

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Recent progress on the effects of structured lipids and fluidity of plasma membrane on tumor metastasis

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Abstract: The lipid composition of cell plasma membranes of aggressive tumors is significantly altered from normal, affecting the membrane fluidity and function. Plasma membrane fluidity involves multiple steps in tumor invasion and metastasis, including cell movement, adhesion, lateral diffusion of membrane molecules, signal transduction, material exchange and so on. This review highlights the difference in plasma membrane lipid composition and fluidity between normal and cancer cells, as well as the correlation with the invasion and metastasis potential of cancer. We also point out that the proliferation, invasion and metastasis of tumors can be inhibited by improving membrane fluidity or interfering with the membrane structured lipid composition, this focusing more on changing the biophysical properties of cancer cell membranes, and providing a novel strategy that works for treatment of tumor metastasis.

Key words: plasma membrane; membrane lipid; lipid raft; membrane fluidity; tumor metastasis

细胞膜是维持细胞完整形态和生命活动的重要基础, 是与外界环境进行物质交换和信息传递的场所[1]。膜脂质构成了细胞膜的基本骨架 (图 1), 膜流动性是细胞膜最直观的物理特征, 对膜的功能特性产生重要影响[2]。细胞膜结构和流动性等理化性质的异常, 可能导致细胞产生一系列病理变化, 乃至机体功能紊乱, 引起各种疾病[3]。肿瘤侵袭和转移是肿瘤患者病情恶化和高死亡率的主要原因。近年来研究发现, 癌变过程中细胞膜构成和流动性相比正常状态均发生了明显变化, 并显著依赖于肿瘤表型[4], 在癌症晚期观察到的膜结构、性质和功能更有利于肿瘤细胞的侵袭[5]。

肿瘤侵袭在细胞层面上涉及的多个步骤被认为依赖于细胞膜流动性, 包括质膜与下层肌动蛋白脱离, 细

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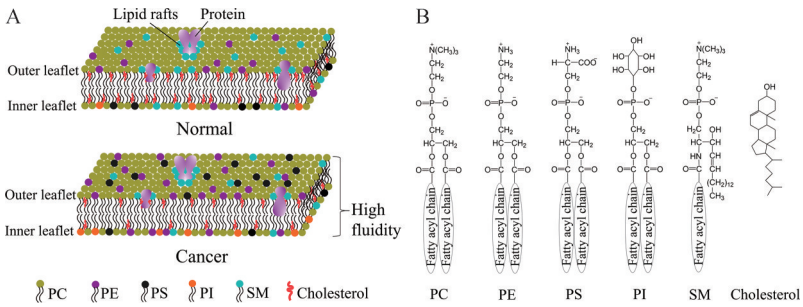

Figure 1　Differences in plasma membrane lipid composition and fluidity between normal and cancer cells (A); structures of plasma membrane lipids (B). PC: Phosphatidylcholine; PE: Phosphatidylethanolamine; PS: Phosphatidylserine; PI: Phosphatidylinositol; SM: Sphingomyelin

胞膜横向扩散能力增强, 对细胞外基质的浸润, 细胞黏附、汇合, 肿瘤细胞增生, 最后入侵组织[6,7]。此外, 膜流动性还影响着细胞骨架的稳定性、膜的通透性、膜分子间相互作用以及配体对细胞表面受体的激活等[7]。可以说, 细胞膜流动性是决定肿瘤细胞侵袭转移的非常重要的生物物理特性。而膜流动性主要取决于膜结构脂质的组成。因此, 全面系统理解细胞膜脂质构成和膜流动性在肿瘤发生发展和侵袭转移过程的作用, 对于恶性转移癌的预防和治疗具有重要意义。本文探讨了肿瘤侵袭转移与膜脂质构成和流动性的关系, 希望能为癌症治疗提供新的思路和理论支持。

1　细胞膜结构脂质

细胞膜是细胞最外层的膜状结构, 也称为质膜 (plasma membrane), 主要由脂质、蛋白质和糖类组成。其中, 脂质可分为甘油磷脂类、鞘脂类和胆固醇等。通常脂质占比最高, 约为40%～50%[8]。

磷脂双分子层是构成细胞膜的基本骨架, 不同蛋白质分子镶嵌其中, 形成一种非均匀的脂质双层流动镶嵌结构[9]。脂质双层膜是不对称的, 表现为外层膜的脂质构成不同于内层膜, 如人红细胞膜磷脂酰胆碱 (phosphatidylcholine, PC) 主要分布于质膜外层, 而磷脂酰丝氨酸 (phosphatidylserine, PS) 几乎完全分布于质膜内层, 内外两层缺乏跨层运动[10]。膜蛋白的种类和含量则与细胞的生理功能密切相关, 细胞功能越复杂, 膜蛋白含量越高[11]。1997年, Simons等[12]提出脂筏模型 (也称为膜筏), 认为胆固醇和鞘脂在膜外层动态聚集形成移动的脂筏, 能够选择性搭载蛋白质, 起到物质运输和信号传导的作用。为了稳定这些功能蛋白, 膜筏结构中积累的胆固醇与其他脂质和筏蛋白相互作用, 形成了液体有序的结构域, 通常表现出比周围膜更低的流动性[13]。质膜流动性是膜上所有结构域流动性的综合体现, 取决于各结构域的分子组成, 特别是脂质组成和蛋白质, 比如胆固醇和其他脂质之间的比例等[6]。并受环境温度影响, 温度增加时膜流动性增加, 温度降低时膜流动性减弱[14]。膜组分的动态变化, 伴随着膜流动性、通透性等膜性质的改变, 以及膜功能的改变, 影响着细胞形态、运动、迁移, 细胞内外物质转运和信息传递等生理过程。

2　恶性肿瘤细胞膜结构脂质的变化

由于宿主的免疫防御机制, 肿瘤转移是个复杂的多步骤过程, 只有那些具有高度转移力的肿瘤细胞才能完成转移, 转移潜力与质膜脂质组成和流动性相关[15]。正常细胞与癌细胞的质膜脂质构成存在差异, 并依赖于肿瘤细胞表型[4]。

2.1　甘油磷脂　甘油磷脂是哺乳动物质膜中最主要的结构脂质, 主要有4种类型: PC、磷脂酰乙醇胺 (phosphatidylethanolamine, PE)、磷脂酰肌醇 (phosphatidylinositol, PI) 和PS。其中, PC含量最为丰富, 是构成磷脂双层膜的主要成分[16]。正常细胞的质膜外单层几乎完全由中性磷脂组成, 包括PC和PE, 大部分为PC。阴性磷脂PS和PI主要分布于靠胞浆的内层[15] (图1)。质膜甘油磷脂的不对称性分布与细胞的功能特性相关[9]。

恶性肿瘤的质膜甘油磷脂变化依赖于其增生、浸润、转移、逃逸等不同阶段的代谢演变[15]。由于快速增殖的肿瘤细胞必须具有较强的生物合成能力和底物可用性, 与之相对应的质膜脂质代谢也呈现出不同程度的激活, 以便为细胞增殖、转移提供必要的膜物质和代谢产物[15,17,18]。PC是细胞膜的主要成分, 在细胞生长发育、信息传导、膜转运、细胞程序性死亡等方面起着重要作用, 其胆碱代谢物即是脂质第二信使, 也是PC合成的前体, 与PC形成代谢循环。PC及其胆碱代谢物均有助于肿瘤细胞增殖生长和程序性死亡[17,19]。PE是仅次于PC的细胞膜主要组分, PE含量增高可影响膜蛋白功能、膜融合、离子跨膜运送等[20], 还可激活蛋白激酶C (protein kinase C, PKC), 从而促进癌细胞生长。

PI对于代谢调控和信号传导具有重要作用[1], 其水解产生的二酰基甘油和三磷酸肌醇 (inositol triphosphate, IP3) 作为第二信使是体内重要的生物活性物质, 都有促进细胞增殖的效应[15]。PS外翻是凋亡细胞早期普遍存在的“吃我”信号, 可被吞噬细胞识别并介导细胞清除[21]。值得注意的是, 虽然PS暴露有利于触发吞噬细胞对凋亡/坏死细胞的识别和清除, 但在肿瘤微环境下, 外翻暴露的PS可通过激活凝血级联, 以及诱导M2样巨噬细胞极化和积累来促进免疫抑制, 从而有利于肿瘤细胞存活与转移[22,23]。有证据显示, PS外翻发生在细胞凋亡之前, 即细胞凋亡与PS外翻是两个彼此独立的事件[24]。

对2-氟苯基乙酰胺 (*N*-2-fluorenylacetamide, 2-FAA) 诱导的大鼠肝增生结节和肝癌组织的质膜脂质分析显示[25], 胆碱类甘油磷脂 (PC和LPC) 与乙醇胺类甘油磷脂 (PE和LPE) 的质膜含量: 肝癌 > 增生结节 > 正常肝, PS含量: 肝癌 < 增生结节 < 正常肝脏。小鼠腹水型肝癌高转移系HCa-P/L6的质膜PE和PI增高, 并显示与肿瘤转移能力增强有关[20]。小鼠胸腺性白血病的质膜PE含量亦有升高[26], 胸腺性白血病细胞膜流动性远高于正常胸腺细胞。Riedl等[27]采用Annexin V荧光标记法比较正常黑色素细胞、非致癌性和恶性黑色素瘤细胞的PS表达, 发现细胞外膜PS表达量与肿瘤恶性程度呈正相关, 高转移系外膜PS表达量是正常黑色素细胞的8～11倍, 但膜PS总量未见增加。以上研究显示, 与正常细胞和低转移系细胞相比, 高转移恶性肿瘤细胞膜的PC、PE、PI含量增高, PS含量不变或减少, 但PS从内膜翻转至外膜的表达量增加。

有趣的是, 恶性肿瘤的质膜脂质与其细胞总含量的变化趋势可能并不一致, 并受机体不同免疫状态影响。与无转移能力的HEP3B人肝癌细胞相比, 转移能力逐渐增强的MHCC-97L和HCC-LM3肝癌细胞的PC总量是逐渐减少的, 硫脂和甘油三酯含量增加[28]。采用^{31}P核磁共振波谱法分析发现, 相比正常乳腺组织和良性肿瘤, 恶性人乳腺癌细胞LPC和LPE总量减少, 而PE、PI含量升高[29]。免疫低下的无胸腺裸鼠肺癌转移灶质膜PE含量则呈现明显降低, LPC增高, 转移灶膜流动性增加[30]。以上研究表明, 虽然恶性肿瘤的质膜PC、PE、PI和外层PS大多呈上调趋势, 但其细胞总量可能存在差异, 需考虑肿瘤类型、分化程度和机体免疫微环境对不同脂质代谢通路产生的影响。在快速增殖过程中, 癌细胞激活的脂质代谢通路面临多种限速步骤, 其胞内合成、转化、转运的激活程度可能并不一致。其结果是, 通过各脂质代谢中间体的稳态水平可能无法准确反映其代谢通量。因此, 有学者提出将代谢组学与基因组学相结合的分析方法[31], 将是解释癌细胞脂质代谢模式异常的一种更有效途径。

2.2 鞘脂类 鞘脂类是以鞘氨醇 (sphingosine, Sph) 而非甘油为基本骨架的一类脂质, 如鞘磷脂 (sphingomyelin, SM)、神经酰胺 (ceramide, Cer)、鞘糖脂、1-磷酸鞘氨醇 (sphingosine-1-phosphate, S1P) 等, 以SM和神经酰胺为主, 脊椎动物的SM占总磷脂的5%～10%[32,33]。SM由脂肪酸、鞘氨醇和磷酸胆碱三部分共价结合形成[28], 优先分布于细胞质膜外层[33]。神经酰胺是SM的一个特殊形式, 结构上以氢代替头部的磷酸胆碱。

鞘脂同时具有膜脂质组分和信号分子的功能, 在细胞增殖、分化、迁移、衰老和凋亡中都发挥着重要调节作用[32,34,35]。在细胞膜上, SM与胆固醇结合形成富含SM的脂筏是各种配体−受体作用的平台, 通过募集受体来调节信号传导, 表达多种细胞功能, 如癌细胞的增殖、转移、炎症和抗癌药耐药等, 并被认为与囊泡的分泌和运输有关[35,36]。神经酰胺则通过在膜上形成富含神经酰胺的平台来充当脂质介质。神经酰胺表现出细胞死亡、细胞周期停滞和自噬诱导等生理作用, 被公认为是一种专一性诱导细胞凋亡的调节剂[36-39]。炎症激活、化疗和过量饱和脂肪酸摄入, 均会导致神经酰胺的合成速率增加[38]。而S1P是鞘氨醇磷酸化的产物, 主要作用于G蛋白偶联受体家族[40,41], 参与细胞增殖、抗凋亡和血管生成等, 对多种肿瘤具有促进作用[38,42-44]。提高S1P可增加人胶质母细胞瘤的侵袭性[45,46]。在细胞死亡和增殖存活中, 神经酰胺与SM和S1P表现出相反的功能作用。因此, 神经酰胺与SM和S1P等相反作用鞘脂之间的平衡稳定性对于细胞命运至关重要[36,38,41,47,48]。

不同鞘脂在各类鞘脂代谢酶的作用下可以相互转化, 形成一个复杂的鞘脂代谢网络, 神经酰胺占据着中心位置, 与SM、鞘氨醇、SIP存在着代谢循环[34,48]: ① 神经酰胺在内质网 (endoplasmic reticulum, ER) 合成, 后转入高尔基体, 在鞘磷脂合成酶 (sphingomyelin synthase, SMS) 作用下合成SM, 然后SM被运输到质膜。质膜SM在鞘磷脂酶催化水解下又可以重新产生神经酰胺。SM是调节神经酰胺释放的储备库[47]。通过SMS合成SM能够减少神经酰胺的产生, 抑制神经酰胺介导的细胞凋亡[49]。② 神经酰胺在神经酰胺酶作用下2位氨基上的脂酰基经催化水解可生成鞘氨醇。鞘氨醇在鞘氨醇酰基转移酶 (也称神经酰胺合酶) 的催化下可再合成神经酰胺。③ 鞘氨醇通过鞘氨醇激酶 (sphingosine kinase, SphK) 磷酸化生成S1P, S1P可经磷酸酶水解逆转化为鞘氨醇, S1P也可经裂解酶分解退出鞘脂循环网络[39,50]。有研究证明, 鞘脂代

谢失常发生在许多癌症中, 并有助于癌症进展和化疗耐药[41]。

对多种恶性肿瘤质膜SM分析显示, 小鼠胸腺性白血病细胞的质膜SM含量较低[26], 2-FAA诱导的大鼠肝增生结节和肝癌组织的质膜SM含量[25]: 肝癌 < 增生结节 < 正常肝脏, 无胸腺裸鼠肺癌转移灶的质膜SM增高[30]。相比正常组织, 人恶性结肠癌淋巴结转移灶的SM含量上升[51]。上述研究显示, 许多癌症的质膜SM水平均发生显著变化, 但不同肿瘤细胞与癌组织转移灶的SM变化趋势似乎存在矛盾和差异。由于SM对胆固醇有较强的亲和力, 两者协同作用可形成特定的膜结构域"脂筏", 作为特殊受体的膜平台在受体激活和细胞信号传导等方面发挥着关键作用[33,36]。不同癌细胞质膜SM稳态水平的差异可能与SM的功能定位、SM消耗及SM与其他鞘脂间的转化有关。

对人转移性结肠癌神经酰胺的分析显示[52], 与正常结肠黏膜相比, 人结肠癌细胞的神经酰胺含量降低了50%以上。采用神经酰胺类似物B13治疗结肠癌细胞肝转移裸鼠, 完全阻止了肿瘤生长。Chen[53]研究发现, 肝癌切除术后, 长链神经酰胺 (C20∶0、C22∶0、C24∶0和C24∶1) 表达下调促进了肝再生组织的肝癌生长, 而短链神经酰胺多为上升趋势。人头颈部鳞状细胞癌中只有一种特异性神经酰胺 (C18∶0) 选择性下调, 推测其与淋巴血管浸润和淋巴结转移相关, 而总神经酰胺含量增加[54,55]。因此, 有研究者认为长链神经酰胺如C16～C24与诱导细胞凋亡配体和细胞损伤相关[56]。由于不同组织神经酰胺的脂肪酸种类繁多, 碳链长度从14～32不等, 可能涉及不同脂酰CoA的作用机制[37], 对于不同恶性肿瘤内源性神经酰胺的种类和水平还需要开展更多研究。目前研究热点主要集中于神经酰胺在促进肿瘤细胞凋亡和抗肿瘤转移方面所发挥的重要作用[57]。

S1P是水溶性较好的单链鞘脂, 可以在膜之间移动, S1P在胞外、胞质、质膜内层、细胞核中均有存在[40]。Huang等[58]采用ELISA法检测子宫内膜癌患者组织匀浆液的S1P表达, S1P水平显著升高, 产生S1P的SphK1活性约是正常子宫组织的2.6倍。Wang等[59]基于质谱分析发现S1P在人类上皮性卵巢癌腹水中表达上调了5～10倍, 生理浓度S1P可促进上皮性卵巢癌和OVCAR3细胞的迁移和侵袭[59,60]。作为生物活性鞘脂, S1P参与细胞增殖、存活和迁移、血管生成和淋巴管生成等重要生理过程, 在许多功能方面与神经酰胺是拮抗的[50]。S1P是一种致癌因子, 大量研究证实S1P对多种肿瘤具有促进作用[44,61]。SphK1是合成S1P的关键酶之一, 在多种类型癌症中过度表达, 包括胃癌、肺癌、肾癌、结肠癌、乳腺癌和前列腺癌等[50]。肿瘤相关细胞因子、生长因子和激素, 如雌二醇、表皮细胞生长因子 (epidermal growth factor, EGF)、胰岛素样生长因子-1 (insulin-like growth factor-1, IGF-1) 和血管内皮生长因子 (vascular endothlial growth factor, VEGF)等, 都会激活SphK以产生S1P[50]。SphK1表达增加与肿瘤进展和预后不良相关[35,50]。

鞘脂代谢网络中, 癌细胞不同鞘脂分子之间的相互转化可以部分解释某些看似矛盾的结果。进一步明确各种鞘脂分子的功能和定位, 鉴定出影响恶性肿瘤发生发展的关键"效应器"[62], 可能是准确理解癌细胞鞘脂代谢模式异常的一种有效途径。

2.3　脂肪酸　磷脂等脂质是由头部基团和多个脂肪酸酰基链组成, 其脂肪酸的长度和不饱和度存在差异, 因此形成的脂质种类繁多[25]。脂质构成决定了膜的物理和功能特性, 其头部基团大多决定细胞内外物质交换和信息传递等特殊生理功能, 而脂肪酸链的长度和不饱和指数往往与细胞膜流动性、肿瘤侵袭转移能力等生物物理特性密切相关。大量研究显示, 相比正常组织, 高转移系癌细胞的质膜不饱和脂肪酸含量明显增加, 参与脂肪酰基链代谢、水解和重塑的酶, 包括硬脂酰辅酶A去饱和酶和几种磷脂酶常在癌组织中异常表达[63-66]。

对2-FAA诱导的大鼠肝增生结节和肝癌组织的质膜脂肪酸含量分析显示[25], C18∶1和C18∶2的百分比: 肝癌 > 增生结节 > 正常肝脏, 而C18∶0和C20∶4的百分比: 肝癌 < 增生结节 < 正常肝脏。随着转移潜能的升高, 肝癌细胞系含棕榈酰 (C16∶0) 的甘油磷脂呈现下调趋势, 用C16∶0处理能显著降低肝癌细胞膜流动性, 抑制细胞葡萄糖摄取和乳酸生成[66]。无胸腺裸鼠肺癌转移灶的质膜磷脂特定不饱和脂肪酸如花生四烯酸和油酸增多, 同时转移灶膜流动性增加[30]。对20例转移的原发乳腺癌患者研究显示[63], 转移病例中磷脂酰胆碱的硬脂酸含量明显低于无转移组。通过敲低硬脂酰辅酶A去饱和酶1 (stearoyl-CoA desaturase-1, SCD1) 可抑制肝癌细胞HCC的侵袭和转移, 而SCD1的过表达或其产物油酸的外源性给药可增强质膜流动性, 挽救HCC的体外侵袭性[67]。上述研究显示, 高转移系癌细胞质膜不饱和脂肪酸含量与质膜流动性呈明显正相关。

2.4　胆固醇　胆固醇是构成细胞膜必需的脂质成分, 对维持膜稳定性和功能都有重要作用。真核细胞的质膜胆固醇含量很高, 可占到总膜脂的50%左右, 在细胞器膜中占比较低, 如高尔基体中约为15%, ER中约为10%, 晚期核内体囊泡的胆固醇摩尔比约为30%[68]。

胆固醇在膜上并非均匀分布, 优先富集于脂筏, 形成有序的微结构域。在膜筏上, 胆固醇通常与鞘脂、锚定蛋白、多种跨膜蛋白等相互作用, 在细胞信号转导和膜转运等多种生物学过程中发挥重要作用[14]。

恶性肿瘤胆固醇的代谢演变与其生理功能相关。富含胆固醇的膜筏是公认的参与细胞信号传导、内外物质转运, 以及介导细胞增殖、凋亡、免疫反应的重要浓缩平台, 包括募集和调节某些对癌细胞增殖、生存、侵袭和转移至关重要的细胞信号蛋白[13,14,69]。胆固醇参与的细胞内吞是摄取营养物质以维持生命代谢活动的重要途径, 包括参与某些癌症的进展[70,71]。网格蛋白、小窝蛋白、巨胞饮及网格蛋白非依赖性载体/GPI锚定蛋白富集的早期内吞室 (clathrin-independent carriers/GPI-AP-enriched early endosomal compartments, CLIC/GEEC) 等多种细胞内吞途径均依赖于胆固醇, 并对胆固醇消耗敏感[71]。胆固醇能够调节膜的刚性、厚度、通透性和流动性等生物物理特性, 对流体质膜表现出致密化作用, 可通过增加磷脂双层的堆积密度, 提高膜的弯曲刚度, 增加局部膜黏度和膜硬度, 降低膜流动性。这种机制可以影响膜内蛋白或其他生物分子的再分布, 使局部膜重组的分子动力学减慢[72]。而膜流动性增加往往是肿瘤细胞具备转移潜能的必要细胞特征[73]。外泌体的形成和释放也依赖于胆固醇参与[74,75]。外泌体是直径约为30～150 nm的微小囊泡, 携带来自母体细胞的脂质、蛋白质和核酸等内容物, 参与细胞间信号传递和大分子物质的转移, 并与癌症进展相关[76]。由ATP结合盒转运蛋白A1 (ATP-binding cassette transporter A1, ABCA1) 介导的胆固醇外排可以促进外泌体释放, 并依赖于高密度脂蛋白 (high-density lipoprotein, HDL) 生成相同的途径[75]。

癌变过程中肿瘤细胞的胆固醇稳态失衡[77], 表现出两种主要特征: ① 胆固醇合成和摄入增强。快速增殖的肿瘤细胞需要合成和摄取大量胆固醇, 以维持其高增长率。一些实体肿瘤如乳腺癌和前列腺癌的细胞胆固醇水平升高[13,77], 胆固醇在恶性组织中积聚[78]。与之对应, 参与胆固醇合成的羟甲基戊二酸单酰辅酶A (3-hydroxy-3-methylglutaryl-coenzyme A, HMG-CoA) 还原酶活性增强或角鲨烯单加氧酶表达增高[78,79]。此外, 参与胆固醇摄取的低密度脂蛋白 (low-density lipoprotein, LDL) 及其受体LDLR在多种癌细胞中过度表达, 包括乳腺癌、肺癌、胰腺癌和白血病等[80,81]。由于富含胆固醇的膜筏是参与细胞信号传导和物质运输的重要平台, 升高细胞胆固醇水平可增加与膜蛋白结合的膜筏含量, 刺激某些信号通路以促进肿瘤细胞生长, 并减少细胞凋亡[13]。② 胆固醇的外排和转运增加。高侵袭性肿瘤的质膜胆固醇含量降低, 细胞膜流动性增加, 肿瘤转移能力增强。从肝癌细胞D23与肝肉瘤细胞MC7分离出的质膜组分显示[82], 细胞膜胆固醇含量显著降低, 且通过荧光偏振法证明了上述两种肿瘤细胞膜的有序性低于正常肝细胞。对2-FAA诱导的大鼠肝增生结节和肝癌组织的质膜分析显示[25], 胆固醇/总磷脂的摩尔比: 肝癌 < 正常肝 < 增生结节。van Blitterswijk等[26]通过荧光偏振法发现小鼠胸腺性白血病细胞质膜胆固醇含量较低, 亚油酸等不饱和脂肪酰基链含量较高。作者把肿瘤细胞膜流动性的增加归因于胆固醇/磷脂的比例降低, 细胞膜无序性增加。Zeisig等[6]发现MT3乳腺癌细胞质膜胆固醇的降低以及不饱和脂肪酸链增多与肿瘤细胞膜流动性增加有关, 而细胞膜流动性增加与体外细胞黏附性增强和荷瘤NOD/SCID免疫缺陷小鼠肺转移增加相关。Sherbet[83]考察了小鼠B16黑色素瘤和L5178淋巴瘤的膜流动性与转移潜力的关系。具有较高转移潜力的肿瘤细胞膜具有较低的胆固醇/磷脂比例和较高的不饱和磷脂含量, 膜蛋白在转移型肿瘤的横向迁移率较高。进一步研究发现, 多种外排和转运途径导致肿瘤细胞质膜胆固醇水平降低。Caveolin-1参与小窝介导的内吞和转胞吞途径, 被认为是细胞内脂质转运系统的一部分, 包括参与ER和caveolae之间的胆固醇转运[84]。有研究证实[85], 过表达caveolin-1的多柔比星敏感和耐药Hs578T乳腺癌细胞质膜胆固醇水平分别降低了约12%和30%, 导致膜流动性增加和脂质堆积密度松动。然而, 两种细胞总胆固醇水平增加了约10%, 这可能与caveolin-1参与胆固醇由胞膜转运至胞质以维持脂质稳态有关。另有证据表明[86], 烟酰胺*N*-甲基转移酶 (nicotinamide *N*-methyltransferase, NNMT) 在高转移的三阴性乳腺癌中过表达, NNMT是通过诱导ABCA1转运蛋白表达来促进胆固醇外排, 增强膜流动性, 促进上皮–间质转化 (epithelial-mesenchymal transition, EMT) 及肿瘤的侵袭和转移。

以上研究显示, 快速增殖的肿瘤细胞其胆固醇的合成、摄取、转运、外排等均有不同程度的激活。增强的胆固醇流入和流出是维持肿瘤细胞增殖和转移所必需的两个代谢途径。

恶性肿瘤细胞膜结构脂质的具体变化见表1[6,13,20,25-30,51-55,58,59,63,66,77,78,82,83,85,87]。

3 细胞膜流动性与肿瘤侵袭

肿瘤组织是由多个细胞亚系组成, 并不是由单一类型的肿瘤细胞构成。这些细胞亚系的转移力并不一致, 只有那些具有高度转移力的肿瘤细胞才能发生侵袭和转移[15]。肿瘤侵袭在细胞层面上的多个步骤被认

Table 1　Deregulation of the plasma membrane lipids of malignant tumors. ↑ Upregulated metabolites; ↓ Downregulated metabolites; HCC: Hepatocellular carcinoma; HNSCC: Human head and neck squamous cell carcinoma; LPC: Lysophosphatidylcholine; LPE: Lysophosphatidylethanolamine; MUFA: Monounsaturated fatty acid; S1P: Sphingosine-1-phosphate; SFA: Saturated fatty acid; UFA: Unsaturated fatty acid

Lipid		Cancer type	Plasma membrane	Cell/Tissue
Glycerophospholipids	PC	HCC	↑[25]	↓[28], ↑[87]
	LPC	HCC, lung (nude mice)	↑[25,30]	
		Breast		↓[29]
	PE	HCC, leukemia	↑[20,25,26]	
		Lung (nude mice)	↓[30]	
		Breast		↑[29]
	LPE	HCC	↑[25]	
		Breast		↓[29]
	PI	HCC	↑[20]	
		Breast		↑[29]
	PS	HCC	↓[25]	
		Melanoma	↑ Outer leaflet[27]	
Sphingolipids	SM	HCC, leukemia	↓[25,26]	
		Lung (nude mice)	↑[30]	
		Colon		↑[51]
	Ceramide	Colon		↓[52]
		HCC		↓ Long-, ↑ short-[53]
		HNSCC		↓ C18∶0, ↑[54,55]
	S1P	Endometrial, ovarian		↑[58,59]
Fatty acid chains	SFA	HCC	↓[25]	↓[66]
		Breast		↓[63]
	UFA	HCC, lung (nude mice)	↑[25,30]	↑ MUFA[87]
Cholesterol		Breast, HCC, leukemia, melanoma, lymphoma	↓[6,25,26,82,83,85]	
		Breast, prostate, colon		↑[13,77,78,85]

为依赖于细胞膜流动性[6,7]。而细胞膜流动性主要取决于其脂质组成, 尤其是胆固醇的占比和脂质不饱和脂肪酸链的多少[65]。大量研究证实, 高转移力肿瘤细胞的质膜胆固醇显著降低, 不饱和脂肪酸酰基链增多, 细胞膜无序性增加, 质膜流动性相应增加[6,7,15,25,26,28,63-65,82]。

有学者对细胞膜流动性影响肿瘤侵袭的机制进行了研究, 涉及以下方面: ① 细胞黏附。质膜流动性和膜筏的异质域结构可以影响配体的聚集, 从而影响肿瘤细胞与内皮的黏附。Zeisig 等[6]比较了指数生长期和汇合条件下的MT3乳腺癌细胞, 融合细胞具有明显更高的质膜流动性, 同时融合细胞膜上的配体运动性更强, 由唾液酸 Lewis X/A 配体介导的细胞黏附性提高了 2 倍。作者认为, 胆固醇的降低和脂质不饱和脂肪酸链的增加, 提高了膜上无序结构域的占比和质膜流动性。增高的质膜流动性能够促进可结合 E-选择素等黏附因子的配体的横向扩散能力, 使配体更容易形成团簇, 在不用增加配体数量的条件下, 提高与内皮细胞受体结合的亲和力, 并以这种方式对乳腺癌细胞的侵袭和转移产生影响。② 促进肿瘤相关生长因子的激活。EGF 对多种上皮细胞具有促细胞分裂增殖的作用, 其受体 EGFR 的过表达与肿瘤恶性程度相关[88-92]。EGFR 为跨膜蛋白, 在质膜上具有侧向流动性。未激活的 EGFR 通常以单体的形式嵌入质膜。只有当配体同时与两个 EGFR 分子相结合, 拉近 EGFR 的胞质部分形成二聚化, 才可活化 EGFR 酶, 然后激活多个下游信号传导途径。已知在癌细胞定向迁移过程中, EGFR 的细胞分布并不均匀, 主要定位于细胞迁移前沿。研究发现[93], EGFR 在迁移细胞上的定位随着细胞膜流动性的变化而显著改变, 其二聚化受到膜流动性的影响。质膜流动性增加有助于 EGFR 二聚化。而通过干扰脂肪酸合成, 如增加长链及多不饱和的脂肪酸, 可降低细胞膜侧向流动性和细胞膜变形性, 减少 EGFR 二聚化, 干扰其向前沿的适当定位, 进而抑制 EGFR 信号级联的激活, 最终减少肿瘤的定向迁移和侵袭。③ EMT 通常被认为是转移的主要驱动因素[94]。细胞膜流动性增加和由此导致的细胞运动能力增强, 与肿瘤细胞干性和 EMT 潜力显著相关[73]。Angelucci 等[95]将 MCF-7 乳腺癌细胞与癌相关成纤维细胞 CAF 共培养, CAF 触发 MCF-7 细胞产生波形蛋白介导的 EMT, 同时荧光探针显示与 CAF 共培养的癌细胞质膜流动性增强。Wang 等[86]认为三阴性乳腺癌中过表达的 NNMT 通过上调 ABCA1 转运蛋白促进胆固醇外排, 增强了质膜流动性, 同时 NNMT 过表达与 N-钙黏

蛋白、波形蛋白和Snail2蛋白等EMT相关信号分子水平呈正相关。可以说, 细胞膜流动性增加是肿瘤细胞具有转移性潜力的必要细胞特征。

4 细胞膜流动性调节与肿瘤抑制

通过调节细胞膜流动性, 可以预防和逆转肿瘤细胞的侵袭转移, 对于抗肿瘤治疗具有重要意义。研究发现, 阿米替林 (amitriptyline) 和氟哌啶醇 (haloperidol) 等某些可抑制EMT的药物能够降低细胞膜流动性、细胞的运动性及肿瘤的干细胞特性, 并抑制体内自发转移。而当保持乳腺癌质膜流动性不变时, 这些抗转移化合物将不再限制转移[73]。由此说明, 膜流动性可能是预防癌症转移的一种可行的治疗靶标[73]。

脂质组成中不饱和脂肪酸和胆固醇的占比是影响质膜流动性的主要因素。当采用饱和脂肪酸如棕榈酸 (C16∶0) 对癌细胞进行处理时, 可显著降低肝癌细胞膜流动性, 抑制肿瘤侵袭能力并减缓裸鼠皮下荷瘤模型中的肿瘤生长速度[66]。另外, 一些靶向可增加质膜硬脂酸组成或抑制SCD1的药物, 也能降低质膜流动性并抑制癌细胞的侵袭[67,96]。有学者将SCD1抑制剂aramchol与酪氨酸激酶抑制剂联用, 可显著增强多纳非尼在HCC肝癌移植瘤模型中的抗肿瘤作用[97]。胆固醇可以增加膜局部刚性和硬度, 并降低膜流动性, 抑制肿瘤侵袭。但由于富含胆固醇的脂筏是参与细胞信号传导、物质交换及各种生化反应的重要平台, 增加膜筏胆固醇含量可能刺激某些有利于促进肿瘤生长、免疫逃逸和细胞耐药的信号通路[13]。因此, 胆固醇作用复杂。增强的胆固醇合成、摄取、转运和外排是恶性肿瘤胆固醇代谢失常的重要特征, 通过靶向特定恶性肿瘤的胆固醇合成、摄取或外排信号通路相关蛋白, 已被证实具有一定抗肿瘤作用[73,98-103]。近年来大量临床研究显示, 他汀类药物可降低大部分癌症的发病率和死亡率, 尤其是肝癌和乳腺癌[98,102,103], 这可能与他汀类药物抑制胆固醇合成和细胞内累积有关。小分子载脂蛋白A1诱导剂apabetalone, 能够降低结直肠癌ABCA1转运蛋白过表达, 通过减少胆固醇外排, 逆转肿瘤恶性表型, 进而抑制结肠癌的增殖、侵袭和转移[104]。

一些天然产物也具有调节细胞膜流动性以改善肿瘤侵袭的能力。有研究报道[105], 表没食子儿茶素没食子酸酯、槲皮苦素、金雀异黄素、大豆黄素等10余种抗肿瘤性植物化学成分以及多柔比星和他莫昔芬等对照药, 在抑制小鼠骨髓瘤细胞增殖的同时, 均降低了细胞膜流动性, 膜流动性的降低通过抑制自由基反应、膜脂质过氧化及膜酶等而起到抗肿瘤作用。葡萄皮提取物中的多酚化合物能降低SCD1水平, 从而降低细胞膜流动性, 抑制Caco-2和SW480人结肠癌细胞的侵袭[106]。

此外, 有些药物虽然不能明确改善侵袭性肿瘤的细胞膜流动性, 但可通过干扰癌细胞增殖和侵袭转移相关的细胞膜脂质组成达到抗肿瘤目的。Wu等[107]观察茯苓多糖 (pachyman polysaccharides, PPS) 对小鼠肉瘤S180细胞、人白血病K562细胞的体外增殖抑制作用。通过分析细胞膜成分发现, 膜胆固醇含量及反映膜流动性的胆固醇磷脂之比C/P值未见明显变化, 但膜唾液酸含量升高, 膜肌醇磷脂的PI转换明显被抑制。且膜磷脂脂肪酸组成发生变化, 花生四烯酸 (C20∶4) 和豆蔻酸 (C14∶0) 降低。提示PPS是通过抑制膜PI转化 (PI→PIP) 和干扰肌醇信息传递系统, 从而抑制癌细胞的快速增殖, 其抗癌机制与膜生化特性改变有关。Petrangeli等[108]评估了锯棕榈脂质甾醇提取物 (lipido-sterolic extract of serenoa repens, LSESr) 对雄激素非依赖性PC3前列腺癌细胞的抗增殖和促凋亡效应。LSESr给药1 h后, PC3前列腺癌细胞的细胞膜组织和流动性发生了复杂变化。膜胆固醇含量减少, 4, 5-二磷酸磷脂酰肌醇 (phosphatidylinositol 4,5-bisphosphate, PIP2) 水平降低, 并与Akt磷酸化减少和细胞凋亡率增高相关, 其原因可能是胆固醇减少导致的细胞增殖相关膜筏的破坏和信号复合物的重新分布。随后, 与膜流动性降低相关的膜饱和脂肪酸/不饱和脂肪酸比率增加, ω6脂肪酸降低, 延长了癌细胞凋亡率和抗肿瘤效果。

由此可知, 影响细胞膜流动性及其膜脂质成分和结构, 可以成为抑制肿瘤增殖、侵袭和转移的一个有效策略。一些靶向细胞膜流动性和膜脂组成的抗肿瘤化合物见表2[66,73,96-100,102-108], 有部分已进入临床研究阶段。

5 结语

尽管转移性癌的死亡率很高, 但目前预防侵袭转移的治疗靶标仍然有限[73]。细胞膜是维持细胞形态和生命活动的重要基础。膜脂质是构成细胞膜的基本骨架, 影响着细胞膜形态和流动性, 以及细胞内外物质交换和信号传导。正常细胞和恶性肿瘤的膜脂质构成和流动性存在差异。细胞膜流动性增加是肿瘤细胞具有转移性潜力的必要细胞特征。本文阐述了肿瘤细胞的膜脂质代谢异常和流动性变化, 及其与癌细胞侵袭转移潜力之间的联系和规律, 并指出靶向细胞膜脂质的一种抗肿瘤转移新疗法, 既通过改善膜流动性或干扰癌细胞增殖侵袭转移相关膜脂质构成达到抗肿瘤目的, 这种思路更侧重于改变细胞膜的生物物理特性, 为预防和治疗癌症转移提供了一种新策略。

Table 2 Anti-cancer compounds that target lipid composition or fluidity of cytoplasmic membrane. AA: Arachidonic acid; EGCG: Epigallocatechin gallate; EMT: Epithelial-mesenchymal transition; ER: Endoplasmic reticulum; HMGCR: HMG-CoA reductase; LSESr: Lipido-sterolic extract of serenoa repens; MACE: Major adverse cardiovascular events; mTOR: Mammalian target of rapamycin; NASH: Nonalcoholic steatohepatitis; OSC: Oxidosqualene cyclase; PIP: Phosphatidylinositol 4-phosphate; PPS: Pachyman polysaccharides; SCD1: Stearoyl-CoA desaturase-1; STAT3: Signal transducer and activator of transcription 3; TK: Tyrosine kinase

Compound	Target	Mechanism	Cancer type	Ref.
Alprostadil, haloperidol, amitriptyline, et al.	Membrane fluidity, ABCA1	Inhibited cell motility and EMT; repressed the metastatic phenotype of cancer; decreased ABCA1 expression and cholesterol efflux	Breast cancer models	[73]
Palmitic acid	Membrane fluidity	Decreased membrane fluidity, reduced malignant cell proliferation, and impaired cell invasion; attenuated phosphorylation levels of mTOR and STAT3 pathway proteins	HCC liver cancer models	[66]
EGCG, quercetin, genistein, daidzein, et al.	Membrane fluidity	Decreased membrane fluidity and suppressed cell proliferation; inhibition of free radicals, membrane lipid peroxidation, and membrane enzymes	Myeloma cells	[105]
SSI-4	SCD1	Suppressed tumor growth; mediated ER stress; in combination with sorafenib, showed a maximum growth inhibition	HCC liver cancer models	[96]
Grape skin extracts	SCD1	Decreased membrane fluidity and inhibited cancer cell migration	Colon cancer cell lines	[106]
Aramchol + donafenib	SCD1 + TK	Combination therapy displayed a potent tumor growth inhibition. Monotherapy of aramchol has no significant anti-tumor effect. Aramchol as an SCD1 inhibitor for therapy of NASH and liver injury (in phase III)	HCC liver cancer models	[97]
Statins	HMGCR	Inhibited cholesterol biosynthesis; inhibited cell proliferation and migration; promoted apoptosis; decreased cancer mortality and longer survival, according to retrospective clinical analysis	Colon, prostate, multiple myeloma and other cancers	[98,99, 102, 103]
Ro 48-8071	OSC	Inhibited cholesterol biosynthesis; decreased cell proliferation and migration; increased apoptosis	HCT116 colon carcinoma and HPAF-II pancreatic adenocarcinoma models	[100]
Apabetalone	ABCA1	Decreased ABCA1 expression and cholesterol efflux; reversed malignant phenotype; decreased cell proliferation and invasion; APOA1 mRNA inducer; apabetalone for therapy of MACE (in phase III)	Colon cancer cell lines	[104]
PPS	Membrane lipid composition	Inhibited cell proliferation; inhibited PI phosphorylation to PIP; modifications in fatty acid composition of phospholipids; decreased AA and myristic acid	K562 leukemia cell and S180 sarcoma cell	[107]
LSESr	Membrane lipid composition	Inhibited cell proliferation and stimulated apoptosis; modifications in phospholipid composition, cholesterol content, the SFA/UFA ratio and membrane fluidity; decreased PIP2 and Akt phosphorylation	PC3 prostate cancer cells	[108]

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