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SPINK在皮肤病中的作用及潜在治疗靶点*

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摘要 丝氨酸蛋白酶抑制剂Kazal型（SPINK）是一种皮肤角质化蛋白酶抑制剂，通过抑制皮肤中失调的组织激肽释放酶（KLKs）来缓解角质细胞过度增殖和改善皮肤状态。在皮肤中，SPINK5、SPINK6、SPINK7和SPINK9等成员各有其独特的功能。*SPINK5*突变或表达异常与一些皮肤病相关，如内瑟顿综合征、特应性皮炎、黑色素瘤等；SPINK6主要在表皮中调节蛋白酶活性，帮助维持皮肤的正常结构与功能，也可促进黑色素瘤转移；SPINK7促进角质细胞异常增殖与炎症反应，这可能是某些炎症性皮肤病的病理过程中的关键因素；SPINK9促进皮肤伤口愈合与抗菌，在皮肤修复和防御机制中扮演重要角色。因此，SPINK家族部分成员是皮肤病潜在的治疗靶点，通过调节皮肤角质化代谢和免疫炎症进程等过程有助于治疗皮肤病相关疾病，未来的研究可能会探索针对SPINK的治疗策略。

关键词 SPINK，皮肤病，组织激肽释放酶，炎症

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丝氨酸蛋白酶抑制剂（serpins）最初在动物血清中发现，广泛存在于动植物、细菌和病毒中[1]，含18个以上非同源家族，其中Kazal型（SPINK）是丝氨酸蛋白酶抑制剂家族中最大的分支，包括SPINK1~14，每个成员含有单个或多个Kazal结构域[2]，具有6个半胱氨酸残基，形成3个分子内二硫键。其在动物组织如精囊、胰腺、体液和皮肤中均存在，并且与纤维蛋白溶解、血凝、胚胎产生、个体发育、炎症和免疫应答等过程密切相关[3]。目前已发现100多种Kazal型蛋白酶抑制剂，它们具有高度可变的活性位点[4]。组织激肽释放酶（KLKs）是丝氨酸蛋白酶家族中的一类，也是表皮屏障功能的关键，参与皮肤脱屑过程。SPINK家族成员与KLKs相互作用[5]，从转录水平、蛋白酶活化和蛋白酶失活水平参与皮肤中KLKs的调节进而改善皮肤状态。SPINK可通过调节丝氨酸蛋白酶活性维持皮肤稳态[6]，能结合丝氨酸蛋白酶的催化位点并抑制它。SPINK家族成员参与多种疾病的发生与发展，如SPINK1、2、4、6、7和13与肿瘤关联密切，其中SPINK13在皮肤肿瘤有一定的相关性[7]，SPINK能够调节精子运输活性[8-9]，维持皮肤屏障功能和角质细胞代谢[10]。SPINK家族突变影响不同疾病，如*SPINK1*突变可减少克罗恩病的发病率，改变慢性胰腺炎进展[11-12]，*SPINK5*突变则增加内瑟顿综合征（Netherton's syndrome）和特应性皮炎患病风险[13]。因此，SPINK与皮肤的病理生理学密切相关。

1 SPINK对皮肤的调控

1.1 SPINK通过抑制KLKs改善皮肤状态

人组织激肽释放酶（KLKs）是一种丝氨酸蛋白酶，参与多种组织生理过程，包括15个成员，具有胰蛋白酶活性和胰凝乳蛋白酶活性[14]。Pampalakis等[15]发现，在健康皮肤中表达的KLKs至少有8种，发挥关键作用的有KLK5、KLK6、KLK7、KLK8以及KLK14[16]。在慢性炎症的环境中，KLK5和KLK7可以刺激其他炎症相关的细胞

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因子的产生，它们过度激活可能加剧慢性炎症[17]，即KLK5被发现能够激活并释放IL-8[18]，KLK7被发现能够激活pro-IL-1β成为IL-1β[19]。KLK6在与恶性进展相关的人类皮肤癌中上调。皮肤中的桥粒黏附分子（DSG1）将皮肤细胞与中间纤维骨架相连，使细胞间的连接更为牢固。皮肤中KLK5、KLK6和KLK14的协同作用会破坏DSG1的稳定性并消除与邻近角质细胞上桥粒胶蛋白的黏附[20]，除此之外，KLKs产生的DSG1蛋白酶水解片段还可能与DSG1及其他黏附分子如E-钙黏蛋白外域片段竞争性结合，干扰正常表皮更新，可能导致过度脱屑和皮肤疾病。

SPINK家族成员调控KLKs活性[21]，其中SPINK5、SPINK6、SPINK9抑制皮肤中KLKs。SPINK5可被弗林蛋白酶切割形成多个丝氨酸蛋白酶抑制结构域，并且与KLKs在皮肤中共定位[22]，可能构成皮肤蛋白水解酶抑制系统，涉及脱屑与细胞脱落，SPINK5缺失型皮肤显著增加胰蛋白酶样或胰凝乳蛋白酶样活性，促使角桥粒钙黏蛋白降解，进而可能引起皮肤疾病。SPINK6是KLKs的选择性抑制剂，与LEKTI-2相似，为广谱蛋白酶抑制剂，具有一个典型的Kazal结构域，全身多部位如面部、手臂、躯干及腿部均可表达，尤以掌跖部位最为突出，能显著抑制KLK2、KLK4、KLK5、KLK7、KLK12、KLK13、KLK14等多种KLKs[23]，尤其对KLK5、KLK7和KLK14的抑制效果较佳。皮肤屏障在机械或代谢刺激下功能障碍，可导致SPINK6表达降低。角质层主要包含不溶性蛋白和脂质，其中SPINK6能抑制皮肤脱屑并且有助于角质层的表皮屏障功能，而表皮转谷氨酰胺酶（TGM）能够促进这种屏障的形成，即不同多肽和鞘脂的谷氨酰胺和赖氨酸残基之间的交联[24]，SPINK6含有赖氨酸和谷氨酸残基，其可以充当TGM的底物，能与TGM1和TGM3在颗粒层和角质层中共定位，这可以使SPINK6交联至细胞外基质蛋白，从而将抑制剂锚定在其作用位点，最终达到调节表皮蛋白酶，维持表皮屏障功能。SPINK9作为KLK5特异性抑制剂，有助于角质层的脱屑过程[25]。*SPINK*基因编码的LEKTI为KLKs家族配体，LEKTI与KLKs在皮肤不同层次独立，在颗粒层共同分泌至细胞间隙[26]。皮肤内，丝氨酸蛋白酶KLKs与角质脱落相关，丝氨酸蛋白酶及其抑制剂间的平衡对维持角质脱落及皮肤屏障功能至关重要，故SPINK可通过调节KLKs的活性从而减少皮肤过度脱屑。

1.2 SPINK7促进角质细胞异常增殖与炎症应答

皮肤病通常表现为细胞过度增殖、分化异常及免疫细胞浸润和炎症因子释放等。白介素-22（IL-22）是一类由Th17和Th22细胞为主的免疫细胞分泌产生，与相关受体结合后能激活传导通路中的信号转导因子，通过与靶基因DNA结合区域相结合而实现相应的生物学效应，参与皮肤病的发病[27]。其在皮肤功能中呈双重性，对角质形成细胞既有保护作用也可能导致损害。一方面IL-22能激发角质形成细胞产生多种免疫调节分子与微生物肽，构建化学防线，还可促进其增殖，抑制分化，助力伤口愈合及本体防御。但另一方面，IL-22在体内过表达的可诱导皮肤细胞显著增生和炎症，在特应性皮炎和银屑病患者皮损处发现IL-22的水平显著升高[28]。Kazal型丝氨酸蛋白酶抑制因子7（SPINK7）又名食管癌相关基因2（ECRG2），是SPINK家族的重要成员，与皮肤组织的炎症性疾病相关。有研究报道SPINK7在银屑病和湿疹等炎症性皮肤病中表达上调[29]。也有实验结果表明，IL-22刺激明显导致人角质细胞内促炎症因子IL-23、TNF-α和IL-17A表达水平显著上升，而*SPINK7*沉默后能够抑制IL-22诱导的角质细胞异常增殖与炎症应答，机制可能与调控Wnt/β-catenin信号通路有关[30]，因此SPINK7有望成为治疗皮肤病新的靶点。

1.3 SPINK9促进皮肤伤口愈合与抗菌

Kazal 9型丝氨酸蛋白酶抑制剂（SPINK9）是角化细胞衍生的阳离子肽，在掌跖表皮上层中含量丰富，也常在慢性单纯性苔藓、光化性角化病和鳞状细胞癌中表达[25]。其与LEKTI的Kazal型结构域具有高度同源性，并且7.7 ku肽还显示出体外针对KLK5的特异性抑制活性[31]。表皮生长因子受体（EGFR）广泛分布于角质细胞表面，并且在增殖的基底细胞层中表达最为显著[32]。EGFR信号转导是由于ADAM家族的金属蛋白酶功能上调而发生的[33]，其在皮肤稳态和伤口愈合中的作用已被确立[34]。SPINK9可以激活嘌呤能P2受体（P2R），触发多种细胞信号通路，如ADAM17依赖性EGFR的磷酸化和细胞外信号调节激酶1/2（ERK1/2）信

号，进而诱导细胞迁移，能对皮肤伤口愈合起到一定作用[35]。除此之外，SPINK9是表皮抗菌肽的成员，人体皮肤屏障功能扮演重要角色，能够对入侵的微生物快速做出反应，并防止外部微生物感染，在特定N端变体通过靶向细胞膜和细胞质表现出对大肠杆菌的杀菌活性，并且杀菌功效受到细菌伴侣SKP耐药性的影响[36]。

2　SPINK家族成员与皮肤病的关系

2.1　SPINK与内瑟顿综合征

内瑟顿综合征是罕见的常染色体隐性遗传病，表现为鱼鳞样红皮病、套叠性并发症（竹节状毛发）及特应性体质，患者皮肤广泛脱屑、发炎、并出现过敏症状和毛发异常，目前尚无令人满意的治疗方法[37-38]。病因与常染色体5q31~q32区域*SPINK5*基因变异关联，由编码丝氨酸蛋白酶抑制剂LEKTI功能缺失或突变导致[39]。*SPINK5*基因编码的LEKTI在皮肤表层细胞中发挥重要的抑制蛋白功能，对抗涉及皮肤脱屑和炎症的13种丝氨酸蛋白酶：胰蛋白酶、类胰蛋白酶、糜蛋白酶、纤溶酶、凝血酶、中性粒细胞弹性蛋白酶、组织蛋白酶G和激肽释放酶1、3、5、7、8和14[40]。LEKTI在表皮颗粒层与角质层界高表达[41]，对皮肤屏障形成及更新至关重要，缺乏会引起角质层附着不良及屏障功能损失，这是内瑟顿综合征的多种临床特征与并发症的原因。同时导致组织激肽释放酶KLK5、KLK7、KLK14以及表皮弹性蛋白酶2（ELA2）过度活跃[42]，KLK5活性过高会激活蛋白酶受体2（PAR-2）导致过敏和炎症的级联反应，即KLK5还会激活KLK7和ELA2导致皮肤屏障缺陷[43]。*SPINK5*基因突变致LEKTI表达量与功能降低，影响角质细胞功能，以及皮肤细胞间黏附减弱，导致屏障受损和感染[44]。目前已经发现34个导致过早终止的密码子的内瑟顿综合征相关*SPINK5*基因突变[45]。可通过鉴定*SPINK5*有害突变和患者的LEKTI免疫组化来诊断内瑟顿综合征[46]。总之，内瑟顿综合征发病机制与*SPINK5*变异有关，该缺陷引致皮肤屏障与免疫应答异常，触发病理反应。

2.2　SPINK与特应性皮炎

特应性皮炎（atopic dermatitis，AD）为慢性炎症性皮肤病，通常起始于婴儿期和儿童早期，典型症状为皮肤干燥、湿疹样皮炎及持续瘙痒[47]，其变态反应特征显著，80%的AD患者血清IgG水平升高[48]。AD发病与皮肤屏障异常、免疫系统功能失调，遗传及环境因素密切相关。AD患者中存在*SPINK5*突变[49]，该基因的33个编码外显子区域存在单核苷酸多态性[50]，部分多态性可能降低LEKTI多肽的免疫抑制作用，即*SPINK5*外显子13和14编码存在于外周血中的纯化肽（HF7665），该肽对丝氨酸蛋白酶具有显著的抑制功能[51]，有研究证明，通过诱导SPINK5可以上调LEKTI，防止皮肤屏障功能受损，破坏患者皮肤中炎症的级联反应[46]。另外，SPINK5多态性与高血清IgE水平相关，可能通过调节血清IgE水平影响皮肤免疫应答[52]。KLK7是皮肤病变中的关键酶，当小鼠过表达KLK7后会出现类似于人类特应性皮炎的相关症状[53]，而LEKTI可抑制KLK7从而抑制丝聚合蛋白（FLG）的降解过程，是保持FLG稳态的关键机制。在AD小鼠模型中，LEKTI可明显降低小鼠皮肤损伤中嗜酸性粒细胞的积累，有利于减轻AD炎症[54]。因此，SPINK5在AD治疗中具有潜在价值。

2.3　SPINK与黑色素瘤

恶性黑色素瘤是起源于神经嵴黑色素细胞的肿瘤，皮肤为主要发病部位，由表皮基底层黑色素细胞恶性转化而来。其发病率近年稳步上升，5年生存率仅为4.6%[55]。该瘤高侵袭高转移，原发灶多在少受紫外线部位。研究表明，SPINK5在恶性黑色素瘤中低表达，其低表达可能促进病变发生[56]，敲低SPINK5可增强肿瘤细胞转移能力，通过STAT3通路间接促进黑色素瘤上皮-间充质转化（EMT），而SPINK5过表达则表现出相反的趋势[57]。*SPINK6* mRNA在肿瘤细胞中上调[58]，尤其是在皮肤黑色素瘤细胞中高表达。有研究发现，SPINK6是黑色素瘤细胞转移所必需的，可激活表皮生长因子受体和人酪氨酸蛋白激酶受体A2（EphA2）以及下游ERK1/2和AKT通路，从而促进黑色素瘤转移[59]（图1）。靶向与免疫治疗能够提高患者生存率。因此，SPINK研究对治疗黑色素瘤有潜在意义。

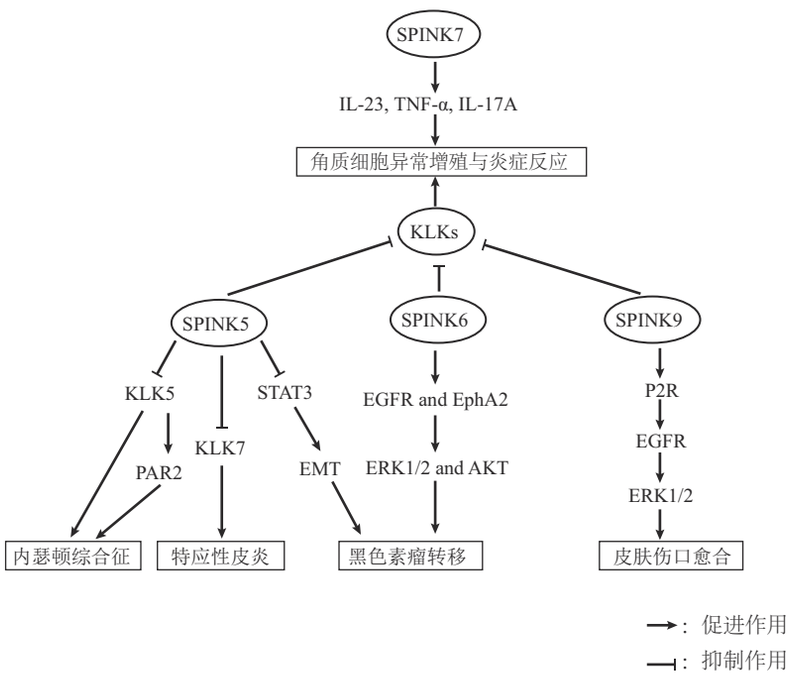

Fig. 1　Mechanisms of signaling regulation of the SPINK in dermatological disorders

图1　SPINK在皮肤病中的信号调控机制

（a）SPINK5可抑制组织激肽释放酶5（KLK5）活性改善内瑟顿综合征，抑制组织激肽释放酶7（KLK7）活性改善特应性皮炎，抑制STAT3通路间接抑制黑色素瘤转移。（b）SPINK6可激活表皮生长因子受体（EGFR）和人酪氨酸蛋白激酶受体A2（EphA2），从而激活下游ERK1/2和AKT通路。（c）SPINK9可激活嘌呤能P2受体（P2R）使表皮生长因子受体（EGFR）磷酸化，从而激活ERK1/2通路促进皮肤伤口愈合。（d）SPINK7可促进角质细胞异常增殖与炎症反应。（e）SPINK5、SPINK6和SPINK9可通过抑制组织激肽释放酶（KLKs）活性来改善角质细胞异常增殖与炎症反应。

3　总结与展望

近年来，SPINK在皮肤疾病中的作用机制愈加受到关注。首先，SPINK主要通过抑制丝氨酸蛋白酶来发挥其生物学功能。丝氨酸蛋白酶在皮肤炎症反应、组织重塑以及细胞生长等过程中发挥作用，SPINK蛋白通过抑制这些酶的活性，能够帮助维持皮肤的屏障功能，防止过度的炎症反应。其次，一些研究结果也表明，SPINK与皮肤微生物群的相互作用可能影响皮肤健康，通过调节微生物群落的组成，间接影响皮肤的免疫状态，从而对皮肤疾病的发展产生影响。最后，在某些皮肤疾病中，SPINK蛋白的表达水平可能会受到干扰，导致皮肤功能下降，这一现象可能会加剧皮肤的炎症和细胞凋亡，进一步引发皮肤病的症状。总之，SPINK家族在人体的诸多生理病理功能起到重要作用，参与了机体的皮肤保护及正常发展。由*SPINK*基因编码的丝氨酸蛋白酶抑制剂LEKTI能够调控表皮中KLKs活性，维持皮肤正常脱屑功能。目前在皮肤中的研究主要集中在SPINK5、SPINK6、SPINK7、SPINK9等。*SPINK5*基因异常在内瑟顿综合征和特应性皮炎等慢性炎症性皮肤病中已得到证实；SPINK6可与表皮转谷氨酰胺酶相互作用共同维持表皮屏障功能，并且在黑色素瘤转移过程发挥一定作用；SPINK7对皮肤细胞起炎症调控作用，但作用机制尚不清晰；SPINK9被证明可以促进伤口愈合，也能产生抗菌作用。

综上所述，SPINK可能成为皮肤病治疗的新靶点，研发相应的小分子抑制剂和单克隆抗体等药物具有治疗皮肤病的潜力，SPINK的研究有助于深入了解皮肤的生理病理过程，通过其功能和调控机制，可以更好地理解皮肤屏障的形成和维持、炎症反应的发生和发展等过程，为皮肤病的预防和治疗提供新的思路和方法。

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Role of SPINK in Dermatologic Diseases and Potential Therapeutic Targets*

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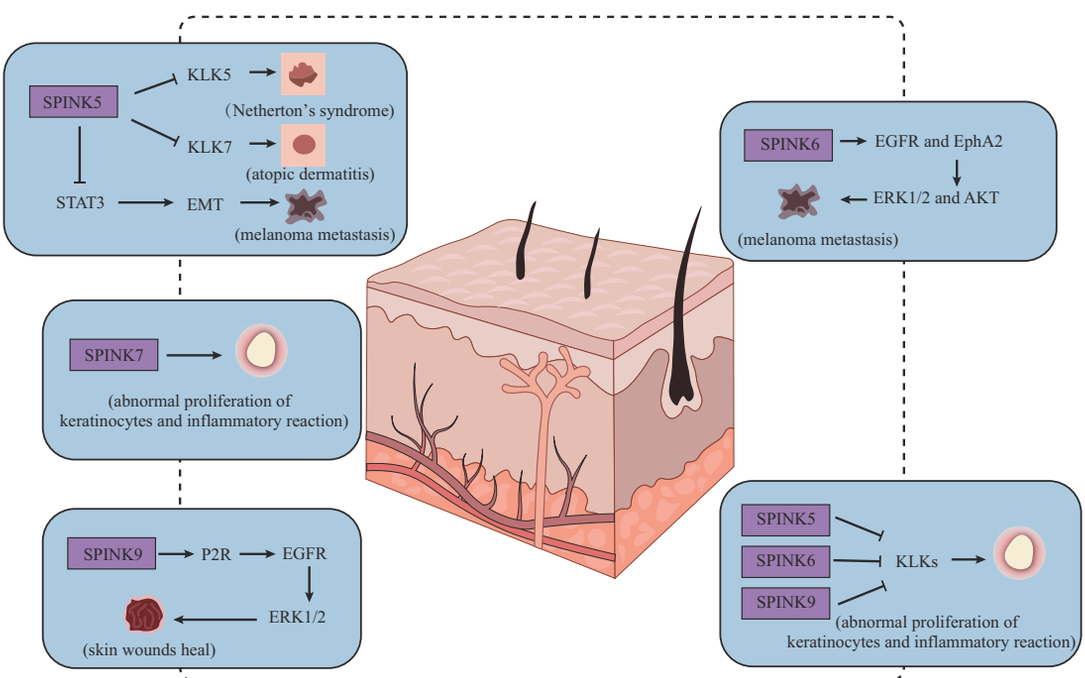
Graphical abstract



Abstract　Serine protease inhibitor Kazal-type (SPINK) is a skin keratinizing protease inhibitor, which was initially found in animal serum and is widely present in plants, animals, bacteria, and viruses, and they act as key regulators of skin keratinizing proteases and are involved in the regulation of keratinocyte proliferation and inflammation, primarily through the inhibition of deregulated tissue kinin-releasing enzymes (KLKs) in skin response. This process plays a crucial role in alleviating various skin problems caused by hyperkeratinization and inflammation, and can greatly improve the overall condition of the skin. Specifically, the different members of the

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SPINK family, such as SPINK5, SPINK6, SPINK7, and SPINK9, each have unique biological functions and mechanisms of action. The existence of these members demonstrates the diversity and complexity of skin health and disease. First, *SPINK5* mutations are closely associated with the development of various skin diseases, such as Netherton's syndrome and atopic dermatitis, and SPINK5 is able to inhibit the activation of the STAT3 signaling pathway, thereby effectively preventing the metastasis of melanoma cells, which is important in preventing the invasion and migration of malignant tumors. Secondly, SPINK6 is mainly distributed in the epidermis and contains lysine and glutamate residues, which can act as a substrate for epidermal transglutaminase to maintain the normal structure and function of the skin. In addition, SPINK6 can activate the intracellular ERK1/2 and AKT signaling pathways through the activation of epidermal growth factor receptor and protease receptor-2 (EphA2), which can promote the migration of melanoma cells, and SPINK6 further deepens its role in stimulating the migration of malignant tumor cells by inhibiting the activation of STAT3 signaling pathway. This process further deepens its potential impact in stimulating tumor invasive migration. Furthermore, SPINK7 plays a role in the pathology of some inflammatory skin diseases, and is likely to be an important factor contributing to the exacerbation of skin diseases by promoting aberrant proliferation of keratinocytes and local inflammatory responses. Finally, SPINK9 can induce cell migration and promote skin wound healing by activating purinergic receptor 2 (P2R) to induce phosphorylation of epidermal growth factor and further activating the downstream ERK1/2 signaling pathway. In addition, SPINK9 also plays an antimicrobial role, preventing the interference of some pathogenic microorganisms. Taken as a whole, some members of the SPINK family may be potential targets for the treatment of dermatological disorders by regulating multiple biological processes such as keratinization metabolism and immuno-inflammatory processes in the skin. The development of drugs such as small molecule inhibitors and monoclonal antibodies has great potential for the treatment of dermatologic diseases, and future research on SPINK will help to gain a deeper understanding of the physiopathologic processes of the skin. Through its functions and regulatory mechanisms, the formation and maintenance of the skin barrier and the occurrence and development of inflammatory responses can be better understood, which will provide novel ideas and methods for the prevention and treatment of skin diseases.

Key words SPINK, skin disease, tissue kallikrein, inflammation
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