·综述·

银屑病发病机制及药物研究新进展

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摘要: 银屑病是一种由多因素诱发的慢性、复发性和炎症性皮肤病, 典型临床表现为鳞屑性红斑或斑块, 并可引起代谢综合征、心血管疾病和炎症性关节炎等多种并发症, 严重影响患者生活质量。对银屑病发病机制的深入了解有助于发现新的治疗靶点及研发有效的新型治疗药物, 因此具有重要的临床意义。本文综述了近年来银屑病发病机制及治疗药物研究的新进展。

关键词: 银屑病; 发病机制; 化学药物; 生物制剂

中图分类号: R967 **文献标识码**: A **文章编号**: 0513-4870(2023)10-2942-10

New advances in the pathogenesis and drug research of psoriasis

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Abstract: Psoriasis is a chronic, recurrent, and inflammatory skin disease induced by multiple factors. Its typical clinical manifestation is scaly erythema or plaques, which can cause various complications such as metabolic syndrome, cardiovascular disease, and inflammatory arthritis, seriously affecting the quality of life of patients. A deep understanding of the pathogenesis of psoriasis is helpful to discover new therapeutic targets and develop effective new therapeutic drugs, thus having important clinical significance. This manuscript reviews the new advances in the pathogenesis and drug research of psoriasis in recent years.

Key words: psoriasis; pathogenesis; chemical drug; biologics

银屑病是一种免疫介导的慢性、炎症性和系统性疾病, 全球患病率约2%～3%, 且近几年呈现逐年上升趋势[1]。其临床表现多样, 典型症状为鳞屑性红斑或斑块, 局限或广泛分布, 根据临床特征分为寻常型、关节病型、疱疹型和红皮病型[2]。银屑病病程长, 易复发, 并可引起多种并发症, 包括代谢综合征、心血管疾病和精神疾病等, 严重影响患者的生活质量[2]。银屑病的病理特征主要为角质形成细胞 (keratinocyte, KCs) 过度增殖引起的表皮增生, 其发病机制复杂, 尚未完全阐明, 环境、遗传和免疫等多种因素共同参与, 尤其是固有免疫和适应性免疫在发病中起到重要作用, 多种免疫细胞和细胞因子与银屑病的病理生理机制密切相关。

银屑病的治疗包括局部治疗、物理治疗和系统治疗。轻度患者以外用治疗为主, 中、重度患者采用外用治疗联合物理治疗/传统系统性药物治疗, 或者单用生物制剂[3]。但这些治疗方法尚不能根治该疾病, 因此对其发病机制的深入了解有助于发现新的治疗靶点及研发有效的新型治疗药物, 具有重要的临床意义。本文综述了近年来银屑病发病机制 (图1) 及治疗药物研究的新进展。

1 银屑病免疫发病机制概述

皮肤由表皮、真皮及皮下组织等结构共同构成, 是机体抵御外界生物入侵的第一道屏障。皮肤功能的稳

收稿日期: 2023-04-17; 修回日期: 2023-05-08.

基金项目: 中国医学科学院医学与健康科技创新工程 (2021-I2M-1-005); 中央高水平医院临床科研业务费 (2022-PUMCH-C-025).

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DOI: 10.16438/j.0513-4870.2023-0468

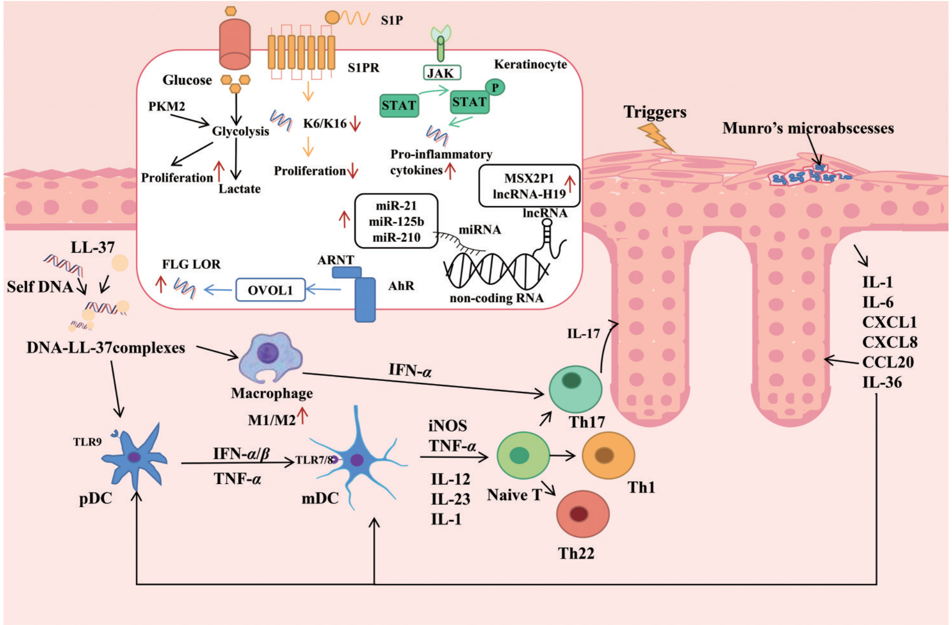

Figure 1 Pathogenesis of psoriasis. Keratinocytes can be stimulated by initial triggers, then stressed keratinocytes release self-nucleotides, which combined with antimicrobial peptide (LL-37), activate pDCs and subsequent mDCs, involving in the initiation phase of psoriasis. In the development phase, adaptive immune responses are activated. The cytokines in the psoriastic lesions activate Th1, Th2 and Th17 cells for production of various cytokines to contribute to amplify the inflammation. The signaling of metabolic, S1P-S1PR, JAK-STAT, AhR pathway and epigenetic are dysregulated in keratinocyte. ① Excessive proliferation of KCs can increase glucose uptake, then significantly level glycolysis up; ② S1P can combined with different S1PR, then regulate KC differentiation and proliferation; ③ Actived JAK-STAT signaling will promote proinflammatory cytokines transcription; ④ AhR pathway can upregulate the expression of FLG and LOR though OVO-1; ⑤ Dysregulated noncoding RNA of KCs. pDCs: Plasmacytoid dendritic cells; mDCs: Myeloid dendritic cells; IFN: Interferon; TNF: Tumor necrosis factor; TLR7/8/9: Toll-like receptors 7/8/9; JAK: Janus tyrosine kinase; STAT: Signal transducer and activator of transcription; S1P: Sphingosine-1-phosphate; S1PR: Sphingosine-1-phosphate receptor; GLUT1: Glucose transporter type 1; PKM2: Pyruvate kinase M2; FLG: Filaggrin; LOR: Loricrin; OVOL1: OVO-like 1

态由KCs与不同免疫细胞、细胞因子及抗菌肽等生物活性物质相互作用而维持。表皮主要由KCs组成，表皮中基底层细胞在正常生理情况下不断分裂，逐渐分化成熟形成KCs，正常KCs更替时间为28天，但银屑病患者KCs增殖加速，使其更替时间缩短至3～4天[4]，因而表皮细胞的成熟受到干扰，导致表皮组织生长与角化紊乱，产生一系列病理现象。

银屑病的发病机制至今仍在不断的探索，早期的研究主要集中于KCs的生长失调，随着研究的深入，人们发现KCs的异常增殖可能是由于固有免疫及适应性免疫紊乱所导致。在2007年Fitch等[5]及Kastelein等[6]发现并提出银屑病发病的“IL-23/辅助性T细胞17 (IL-23/Th17) 通路”理论[7]，这一信号通路至今仍是银屑病发病机制研究的核心理论及药物研发的重要靶点。局部因素 (皮肤损伤等)、系统因素 (感染等)、药物及心理压力等是银屑病的诱发因素。在银屑病发病早期阶段，在受到易感因素的刺激后，KCs分泌过量的抗菌肽，如cathelicidins (LL-37)、β防御素和S100蛋白等[8]。LL-37能够与受损细胞的自身遗传物质结合形成复合物，LL-37-DNA复合物激活浆细胞样树突细胞 (plasmacytoid dendritic, pDCs) 中的TLR9受体，使其分泌大量干扰素-α (interferon-α, IFN-α) 和IFN-β，既能够调节T细胞发育成熟，又是银屑病发病的起始因子，介导局部髓样树突细胞 (myeloid dendritic cells, mDCs) 活化和成熟，进一步引起银屑病下游炎症反应[9]。活化的mDCs随后分泌如TNF-α、IL-23和IL-12等细胞因子，并且表达一氧化氮合酶，产生一氧化氮，引起炎症、表皮增生及诱导辅助T细胞分化为多个辅助性T细胞亚群[8]。IL-23、IL-1β、TGF-β和IL-6能够诱导Th17细胞活化，TNF-α和IL-6能够诱导Th22活化，这些T细胞亚群迁移至银屑病皮损处，活化的Th1细胞释放IFN-γ和TNF-α，Th17细胞分泌IL-17，随后刺激KCs增殖和分化受损[10]。KCs继而进一步释放抗菌肽和趋化因子，招募免疫细胞聚集，使银屑病疾病的持续及恶化[8]。

目前，多个细胞因子的靶向治疗已在银屑病中显示出良好的疗效，包括TNF-α、IL-23和IL-17单克隆抗

体治疗。TNF-α出现在银屑病发病过程中的多个环节, 能够由多种免疫细胞 (T细胞、DCs和KCs) 释放, 它具有促炎活性, 能够与其他细胞因子相互作用而起到放大炎症的作用, 是IL-23/Th17轴上游的细胞因子, 也能够诱导DCs产生IL-23[9]。IL-23的作用与IL-17密切相关, IL-23可以促进Th17细胞的增殖分化, 而IL-17则主要对KCs发挥促炎作用, 诱导KCs产生促炎趋化因子CCL20, 招募Th17和mDCs聚集[11]。

如何打破银屑病中的这一恶性循环将是银屑病治疗及药物研发中的重要思路。目前机制研究主要在这一核心环节的基础上进行深入和延伸性研究。

2 银屑病发病机制新进展

2.1 IL-36

近年研究发现, 不同于其他类型的银屑病, 在脓疱型银屑病中细胞因子IL-36发挥更为重要的作用。IL-36是IL-1超家族的成员, 包括IL-36α、IL-36β、IL-36γ和IL-36受体拮抗剂 (IL-36 receptor antagonist, IL-36RN), 它们都可以与IL-36受体 (IL-36 receptor, IL-36R) 结合, 其中IL-36RN是IL-36α、IL-36β和IL-36γ的天然拮抗剂[12]。在银屑病患者皮损部位和血清中, IL-36的表达水平显著升高, 且与疾病严重程度呈正相关, 编码IL-36RN的基因*IL36RN*发生突变或缺失可导致脓疱型银屑病的发生[13,14]。IL-36主要在上皮细胞和免疫细胞中表达, IL-17、TNF-α及IL-36自身可诱导其表达增加, 与其受体IL-36R结合后可激活NF-κB和MAPKs信号通路, 促进细胞因子 (IL-1β、IL-6、IL-12、IL-23、TNF-α等)、中性粒细胞趋化因子 (CXCL1、CXCL2、CXCL6、CXCL8等)、淋巴因子 (CCL20、CCL3等) 和共刺激分子等的表达和分泌, 作用于树突状细胞、中性粒细胞及T细胞等, 诱导T细胞增殖、中性粒细胞和Th17细胞募集及活化, 以及大量细胞因子的进一步分泌, 在银屑病皮损中形成持续活化的炎症环路[12]。在咪喹莫特 (imiquimod, IMQ) 诱导的银屑病小鼠模型中, 全身性以及KCs特异性IL36R$^{-/-}$小鼠的银屑病样病理改变均较野生型小鼠显著改善, 且皮损部位中IL-17A、IL-17C、IL-22和IL-23等细胞因子的mRNA水平亦显著降低[15]。因此, 针对IL-36或其相关通路中关键分子的药物是治疗脓包型银屑病的新方向。IL-36R单克隆抗体spesolimab (司柏索利单抗) 已在中国和美国上市, 用于成人泛发性脓疱型银屑病 (generalized pustular psoriasis, GPP) 治疗, 可有效快速地治疗GPP患者的急性发作, 并在长达12周内维持治疗效果[16]。

2.2 表观遗传调控

表观遗传是指在不影响DNA序列改变的前提下, 引起基因表达稳定可遗传改变。与银屑病相关的表观遗传学机制涉及DNA甲基化、组蛋白修饰和非编码RNA (non-coding RNAs, ncRNAs) 等。

2.2.1 DNA甲基化 DNA甲基化指一个甲基基团在DNA甲基化酶 (DNA methyltransferases, DMNTs) 作用下与基因组CpG二核苷酸的胞嘧啶环5′-末端共价结合。目前, 已在银屑病患者皮肤中开展包括全基因组水平和特定基因位点甲基化分析[17]。与健康对照相比, 银屑病患者皮损部位的全基因组甲基化水平明显升高, 且与银屑病皮损面积和严重程度指数 (psoriasis area and severity index, PASI) 评分呈正相关[18]。另一项针对银屑病患者皮损组织的全基因组DNA甲基化研究发现了1 108个差异显著的甲基化位点, 其中12个位点对应的基因与表皮分化相关, 使用TNF-α治疗1个月可使甲基化水平恢复至非银屑病状态[17]。此外, 多项研究揭示银屑病患者皮损组织中存在差异甲基化基因位点, 主要涉及细胞增殖、凋亡、细胞周期及免疫系统调节等[19]。高甲基化的基因包括*PDCD5*、*TIMP2*、*SELENBP1*、*CARD14*、*KAZN*、*ECE1*、*MAN1C1*、*DLGAP4*和*SFRP4*等, 低甲基化的基因包括*S100A9*、*PTPN22*、*CYP2S1*、*EIF2C2*、*SHP-1*和*HLA-DRB1*等, 它们的甲基化水平均与基因表达负相关[20,21]。HLA-C的高甲基化水平以及p16的低甲基化水平与PASI评分呈正相关[19]。与银屑病特征性组织病理学变化 (如Munro′s微脓肿、表皮突延伸等) 相关的差异甲基化基因的鉴定提示DNA甲基化可能介导银屑病的病理改变[20]。

在免疫细胞中亦开展DNA甲基化分析。银屑病患者外周血单个核细胞 (peripheral blood mononuclear cell, PBMC) 全基因组甲基化水平显著高于健康对照, 此项研究还发现, 银屑病患者PBMC中DNMT1呈高甲基化, 而MBD2和MeCP2呈低甲基化[18]。两个研究团队分别报道了银屑病患者CD4$^+$ T细胞中升高和降低的全基因组甲基化水平[22,23]。此外, 银屑病患者Tregs细胞中FOXP3的甲基化水平显著高于健康对照, 这导致FOXP3表达降低, Tregs细胞数目减少, 从而促进银屑病的发生发展[24]。上述研究揭示, 靶向DNA甲基化在银屑病治疗中的潜能, DMNT抑制剂阿扎胞苷可以改变银屑病患者CD4$^+$ T细胞中相关基因的甲基化水平和表达[19]。靛玉红可通过抑制DNMT1的活性从而减少WIF1启动子区域甲基化水平, 抑制KCs增殖和诱导凋亡, 从而改善IMQ诱导的小鼠银屑病模型症状[24]。

2.2.2 组蛋白乙酰化 组蛋白氨基末端的赖氨酸乙酰化是高度动态的, 乙酰化修饰可中和组蛋白的正电荷, 疏松染色质结构, 总体上活化转录。银屑病患者

PBMC中组蛋白H4乙酰化水平低于健康对照PBMC, 且乙酰化水平与PASI评分呈负相关[17,25], 提示组蛋白乙酰化机制可能在银屑病中发挥作用。组蛋白乙酰化转移酶 (histone acetyltransferases, HATs) 和组蛋白去乙酰化酶 (histone deacetylases, HDACs) 分别催化组蛋白的乙酰化和去乙酰化, 因此可作为药物治疗的靶点。在银屑病患者的PBMC和皮损组织中, HDAC1表达明显增加, 而III类HDAC SIRT1的表达水平显著降低[26]。抑制HDAC可通过增加FOXP3的表达而调节Treg细胞功能, 阻止Treg细胞向致病性Th17细胞分化[27,28]。而活化SIRT1可在KCs中发挥抗炎和促凋亡作用[24], SIRT1激动剂白藜芦醇可改善IMQ诱导小鼠银屑病模型的皮损严重程度和病理组织学损伤[29]。选择性SIRT1激动剂SRT2104的II期临床试验显示了其对银屑病的良好疗效和安全性[30]。

2.2.3 ncRNAs 微小RNAs (microRNAs, miRNAs) 是一类非蛋白质编码的小分子单链RNA。目前已发现超过250个miRNAs在银屑病中异常表达[31], 它们通过调节靶基因参与KCs增殖和分化、细胞因子和趋化因子产生以及免疫炎症反应等相关信号通路, 从而在银屑病的发生发展中发挥重要调控作用 (表1)[31-33]。此外, miRNAs (尤其循环miRNAs水平) 还可以作为银屑病诊断、监测治疗反应及评价预后的生物标志物[34]。多项细胞或动物实验结果表明, 调节某些miRNAs (如抑制miR-21、miR-31或miR-210, 增加miR-125b等) 具有良好疗效[35-38], 提示靶向miRNAs有望成为银屑病治疗的新方向, 但仍需进一步的深入研究。

长链非编码RNAs (long non-coding RNAs, lncRNAs) 是一类长度大于200个核苷酸的非蛋白质编码RNA, 通过结构相互作用和/或互补碱基配对与DNA、RNA或蛋白质相互作用, 从表观遗传修饰、转录、转录后、翻译和翻译后等不同层面调节基因表达[39]。lncRNAs在KCs分化、黑色素细胞功能、毛发生长及伤口愈合等皮肤生理过程中发挥重要调节功能[32]。多项研究通过微阵列或高通量RNA测序技术发现超过4 000个lncRNAs在银屑病患者皮损组织中差异表达, 与KCs分化、细胞增殖和凋亡及炎症免疫反应等相关[40-42]。与银屑病相关的重要lncRNAs如表2[33]所示。与miRNAs相比, lncRNAs与银屑病相关性研究尚处于早期阶段, 对lncRNAs功能鉴定及其在银屑病发病机制中作用的深入了解将为开发靶向治疗药物提供理论基础。

2.3 JAK-STAT通路

JAK-STAT通路包含3个主要组成成分: 酪氨酸激

Table 1 Main microRNAs altered in psoriasis[31-33]. KCs: Keratinocyte

Name	Level	Target	Function
miR-17-92	Upregulated	CDKN2B; SOCS1	Regulate KCs proliferation and cell-cycle progression
miR-125a	Downregulated	CAMK4	Inhibit KCs proliferation and enhance apoptosis
miR-125b	Downregulated	FGF2; USP2; BRD4	Regulate KCs proliferation
miR-203	Upregulated	TNF-α; IL-24; SOCS-3	Regulate the balance of KCs differentiation and proliferation
miR-21	Upregulated	TIM3	Promote inflammation and inhibit apoptosis
miR-187	Downregulated	CD276	Inhibit KCs proliferation
miR-383	Downregulated	LCN2	Regulate KCs proliferation and apoptosis
miR-210	Upregulated	FOXP3	Induce Th17 and Th1 cell differentiation, inhibit Th2 differentiation
miR-142-3p	Upregulated	SEMA3A	Regulate KCs proliferation and apoptosis
miR-145-5p	Downregulated	MLK3	Suppress KCs proliferation and secretion of chemokines
miR-146a	Upregulated	IRAK1; TRAF6; CARD10; FERMT1	Inhibit psoriasiform inflammation and neutrophil infiltration
miR-146b	Upregulated	CARD10; FERMT1; IRAK1; TRAF6	Regulate inflammatory response and KCs proliferation
miR-146a/b	Upregulated	CARD10; FERMT1; IRAK1; TRAF6	Regulate psoriatic inflammation with SERPINB2
miR-155	Upregulated	PTEN	Inhibit KCs proliferation and promotes apoptosis
miR-193b-3p	Downregulated	ERBB4	Inhibit psoriatic inflammation through NF-κB/STAT3 signaling
miR-194	Downregulated	GRHL2; SOX5	Regulate KCs proliferation and differentiation
miR214-3p	Downregulated	FOXM1	Inhibit KCs hyperproliferation and psoriasiform inflammation
miR-215-3p	Downregulated	DYRK1A	Inhibit proliferation and cell cycle progression of KCs
miR-340	Downregulated	IL-17A	Reduce psoriatic symptoms
miR-221/miR-222	Upregulated	TIMP3	Increase KCs proliferation
miR-223	Upregulated	PTEN	Regulate KCs proliferation and apoptosis
miR99a	Downregulated	IGF-1R; FZD5; FZD8	Inhibit KCs proliferation and promote terminal differentiation of KCs
miR-424	Downregulated	MEK1 CCNE1	Regulate KCs proliferation
miR486-3p	Downregulated	K17	Mediate keratin 17 expression and KCs hyperproliferation
miR-489-3p	Downregulated	TLR4	Inhibit KCs proliferation
miR-876-5p	Downregulated	ANGPT1	Inhibit KCs proliferation
miR-4516	Downregulated	FN1; ITG9; STAT3	Inhibit KCs migration and suppress genes regulating cytoskeletal reorganization

Table 2 Main long non-coding RNAs (lncRNAs) altered in psoriasis[33]

Name	Level	Target	Function
MSX2P1	Upregulated	miR-6731	Regulate KCs proliferation
lncRNA-H19	Upregulated	miR-130b	Regulate KCs proliferation
PRINS	Downregulated	miR-124; miR-203; miR-129; miR-146a; miR-9 GIP3	Regulate KCs proliferation and apoptosis
MEG3	Downregulated	miR-21	Suppress proliferation and promote apoptosis
LINC00941	Downregulated	SPRR5	Suppress KCs proliferation

酶相关受体、JAK激酶及转录因子STAT, 能够将胞外化学信号传导至细胞内, 从而调节细胞生长、分化及响应病原信号。*STAT3*、*TYK2*、*IL23A*和*IL23R*的基因多态性已被确定为银屑病的易感性因素[43]。银屑病中重要细胞因子IL-23与其受体结合后, 促使JAK1/JAK2/TYK2复合物形成, 继而使STAT3/STAT4磷酸化和二聚化, 并转位进入细胞核, 与相应靶基因启动子结合, 诱导IL-17、IL-21、IL-22和IFN-γ等细胞因子表达和分泌[44]。此外, 活化的STAT3还促进了与Th17细胞分化、激活和增殖相关的多个关键基因的转录。银屑病中其他重要细胞因子发挥致病作用亦通过JAK-STAT通路介导: IFN-γ受体激活后诱导JAK1/JAK2活化和STAT1的二聚化, IL-12受体激活后诱导JAK2/TYK2活化和STAT4的二聚化, 从而促进Th1反应; IL-4受体激活后诱导JAK1/JAK3活化和STAT6的二聚化, 促进Th2反应[44]; IL-6和IL-21可以激活STAT3增强Th17细胞产生IL-17, 进一步放大炎症[45]。KCs受到IL-22刺激后能够激活STAT3信号引起KCs过度增殖及抑制其分化, 在小鼠模型中表现出棘皮病和皮肤炎症的症状[46]。还有研究发现, STAT3的活化会抑制KCs的分化、促进其增殖和分泌抗菌肽, 在过表达STAT3的转基因小鼠中出现银屑病相关症状[47]。JAK1的表达与PASI评分呈正相关[48], JAK1和STAT3组织表达可以作为银屑病严重程度的标志物[49]。因此, JAK-STAT信号通路是银屑病药物研发的重要靶点之一。已有多个JAK抑制剂在斑块型银屑病中开展临床试验, 也表现出良好的疗效, 两项III期随机对照临床试验显示, 当患者每天两次服用5和10 mg托法替布治疗时, PASI明显减少, 高达75%, 以剂量依赖性的方式改善[50]。

2.4 芳香烃受体 (aryl hydrocarbon receptor, AhR)

AhR是一类胞内配体激活受体及转录因子, 在皮肤中广泛表达, 能够感受多种内源性和外源性配体分子, 通过调节环境毒素代谢、光诱导反应、氧化应激、KCs分化、皮肤屏障功能、色素沉着及皮肤免疫网络等, 在维持皮肤稳态中发挥重要作用[51]。研究显示, AhR激活后产生有害还是有益的生物学效应取决于皮肤状态 (健康或炎症) 以及配体的来源或性质[51]。在银屑病患者及小鼠银屑病模型中, Th17细胞都高表达AhR, 并且研究发现Th17细胞产生IL-22依赖于AhR[52,53], 这表明AhR与Th17分泌细胞因子密切相关。此外, 在银屑病患者皮损处KCs中也检测到了AhR的过度表达[54]。这些证据都表明, 银屑病中AhR信号通路过度激活。然而, 在IMQ诱导的小鼠模型中, 敲除AhR会导致*IL-22*、*IL-17*和*IL-23*基因表达上调和皮肤炎症的加剧[55]; 腹腔注射AhR受体激动剂6-甲酰基吲哚并[3,2-B]咔唑 (FICZ) 可以缓解银屑病小鼠症状[56]。AhR在KCs中还能够调节多个终末分化蛋白如丝聚蛋白 (filaggrin, FLG) 和兜甲蛋白 (loricrin, LOR) 的表达, 使用内源性AhR配体激动剂能够使FLG、LOR的表达上调, 因此AhR的激活有助于KCs的分化成熟[52,57,58]。这表明AhR信号通路可能在银屑病中发挥“双刃剑”的作用, 其作用的深入探究有利于银屑病的临床诊治。

目前, 国产新药本维莫德 (Tapinarof) 乳膏作为全球首个AhR激动剂于2019年在中国获批上市, 并于2022年被美国食品药品监督管理局 (Food and Drug Administration, FDA) 批准上市, 用于局部治疗成人轻至中度稳定性寻常型银屑病[59]。

2.5 Rho相关激酶2 (Rho-associated kinase 2, ROCK2)

ROCK属于AGC蛋白激酶家族, 包括ROCK1和ROCK2两种亚型, 是一种丝氨酸/苏氨酸激酶, 它可以被Rho GTP酶激活, 进而磷酸化其底物而发挥生物学作用, 抑制ROCK2能够阻断IL-23/Th17在银屑病中的作用。近年研究发现, ROCK2在调节自身免疫和炎症中发挥重要作用。在健康志愿者$CD4^+$ T细胞中, 使用抑制剂或siRNA拮抗ROCK2可通过抑制转录因子STAT3、IRF4和RORγt减少IL-17和IL-21分泌[60]。在ROCK2抑制剂KD025的II期临床试验中, KD025可降低银屑病患者外周血中IL-17和IL-23水平, 减少皮损部位的表皮厚度、角蛋白16表达和T细胞浸润, 并能够改善PASI评分[61]。但是目前对于这一靶点机制及靶向药物的临床研究尚且有限, 需要进一步研究验证其在银屑病治疗中的可行性。

2.6 鞘氨醇-1-磷酸 (sphingosine-1-phosphate, S1P)/S1PR

S1P是由鞘氨醇激酶 (sphingosine kinase, SPHK) 催化鞘磷脂代谢产生的一种生物活性脂质, 它既能作

为细胞内第二信使, 亦能被分泌到细胞外, 与细胞膜上的S1P受体 (S1PR) 结合后, 通过激活下游信号通路从而调节细胞增殖、分化、凋亡、血管生成和炎症反应等生物学过程[46]。银屑病患者血清中S1P的表达升高, 而使用生物制剂治疗后S1P的循环水平并未降低[62]。这一信号通路在银屑病中的作用还有待探究。Liao等[63]发现S1P能够诱导Th17的分化, 但是对于KCs来说, S1P能够抑制KCs增殖并且诱导其分化, 抑制KCs周期蛋白表达, 并且上调KCs的早期及晚期分化标志物[64,65]。此外S1P还能够通过激活S1PR3短暂增加Ca^{2+}浓度, 而Ca^{2+}对于KCs的分化是必需的[66]。对于KCs增殖的抑制作用则是通过延长ERK蛋白的激活和短暂失活Akt而发挥作用[67]。在IMQ小鼠模型中, 局部直接给予S1P能够减少小鼠炎症反应并且减轻表皮过度增殖[68], 提示局部使用S1P可能起到缓解银屑病的作用, 但是为什么银屑病患者S1P循环水平升高以及S1P是否以不同方式调节KCs和免疫细胞还有待深入研究。

S1PR属于G蛋白偶联受体, 包括5种亚型S1PR1～5[46]。不同的S1PR受体可能在银屑病中发挥不同作用, 其中S1PR1对淋巴细胞迁移的调节作用最强, 激动S1PR1可使大部分循环淋巴细胞被隔离在淋巴结中, 降低外周淋巴细胞数目及淋巴细胞向外周组织运输[46]。目前Ponesimod (ACT128800)、SCD-044及国内研发的艾托莫德和CBP-307等S1PR1激动剂已开展以银屑病为适应症的I期或II期临床试验[69]。

2.7 代谢异常

银屑病中KCs的糖代谢异常和过度增殖与肿瘤细胞类似, 葡萄糖摄取增加, 糖酵解水平显著增高, 从而产生大量ATP和中间代谢产物, 促进KCs增殖, 葡萄糖转运蛋白1 (glucose transporter 1, GLUT1) 和糖酵解限速酶M2型丙酮酸激酶 (pyruvate kinase M2, PKM2) 的表达水平在银屑病患者及IMQ诱导的小鼠模型的皮损处明显增高, 抑制GLUT1或PKM2可抑制KCs增殖[70]。此外, 在IMQ诱导的银屑病模型中, 使用GLUT1敲除小鼠或药理抑制剂, 以及使用PKM2抑制剂或糖酵解抑制剂2-脱氧-*D*-葡萄糖 (2-deoxy-*D*-glucose, 2-DG) 均可明显减轻银屑病样的表皮增生和皮损表现[71,72]。

近年研究亦揭示了银屑病中氨基酸代谢异常, KCs中精氨酸代谢通路的异常是产生银屑病自身抗原的重要原因[73]。此外, 在银屑病患者和IMQ诱导的小鼠模型皮损部位的T细胞中, *L*-型氨基酸转运体1 (*L*-type amino acid transporter 1, LAT1) 的表达水平明显增加, LAT1通过PI3K/Akt/mTOR通路促进IL-17$^+$ $\gamma\delta$T细胞和Th17细胞的增殖以及IL-17、IL-22的分泌, 而LAT1抑制剂JPH203可使IMQ诱导的小鼠银屑病样皮损明显好转[74]。上述结果提示, 靶向异常代谢有望成为治疗银屑病的新策略。

2.8 昼夜节律

昼夜节律调控着皮肤的状态与机能, 随着昼夜节律调控机制的揭示, 近年有研究报道, 银屑病的发生与昼夜节律具有关联。流行病学调查显示, 昼夜节律的破坏增加了银屑病的发病风险, 与银屑病发病密切相关的细胞因子的分泌如IL-17、IL-6和IL-1β等也具有昼夜节律性[75]。此外, 在银屑病患者的皮损和非皮损皮肤中均能检测到昼夜节律调控基因表达的变化。生物钟基因REV-ERB和ROR在抗炎与免疫调节中发挥重要作用, REV-ERB的合成拮抗剂能够抑制$\gamma\delta$T细胞产生IL-17, 从而缓解银屑病小鼠模型症状[76]。昼夜节律是银屑病研究中的一个新方向, 还需要更多的研究来阐释其中的关联。

3 治疗药物进展

3.1 化学药物研究进展

银屑病的外用药物包括润肤剂、保湿剂、维生素D3衍生物、维A酸类、糖皮质激素、钙调磷酸酶抑制剂、AhR激动剂、抗人IL-8单克隆抗体和焦油制剂等。传统系统治疗药物主要包括维A酸类、甲氨蝶呤和环孢素等[3]。近年来, 银屑病发病机制研究取得的进展为外用药物和系统治疗药物提供了新的靶点, 靶向磷酸二酯酶4 (phosphodiesterase 4, PDE4)、JAK/STAT、ROCK2、S1PR1、维A酸受体相关孤儿受体 (retinoic acid receptor-related orphan receptor, ROR) γt、血管生长因子 (vascular endothelial growth factor, VEGF) 受体、原肌球蛋白−受体−激酶A (TrkA)、腺苷A3受体、神经激肽1受体 (neurokinin-1 receptor, NK1R)、受体相互作用蛋白激酶1 (receptor-interacting protein kinase 1, RIPK1)、核因子E2相关因子2 (nuclear factor E2-related factor 2, NRF2) 等[77]致病信号通路中关键分子的治疗策略取得较大成功, 为银屑病治疗带来曙光。其中, 口服PDE4抑制剂阿普米司特已在国内、外上市, 用于斑块状银屑病治疗, 另一个PDE4抑制剂罗氟司特乳膏被美国FDA批准用于银屑病的外用治疗; JAK1/3抑制剂托法替布在2017年被美国FDA批准用于治疗银屑病关节炎; 首款口服选择性TYK2抑制剂deucravacitinib (BMS-986165) 在2022年被美国FDA批准用于斑块状银屑病治疗; 针对其他靶点的候选药物也已进入临床研究阶段 (表3)。

3.2 生物制剂研究进展

生物制剂在中重度银屑病中的应用, 使其治疗和

Table 3　Summary of new chemical treatments under clinical trials for psoriasis

Target	Dosage form	Stage	Name
PDE4 inhibitor	Topical	I	MK-0873
PDE4 inhibitor	Topical	II	Crisaborole (AN2728)
PDE4 inhibitor	Oral	II	Orismilast (IBI353)
PDE4 inhibitor	Oral	III	Hemay005
Pan-JAK inhibitor	Topical	I	PF-06263276
Pan-JAK inhibitor	Oral	II	Peficitinib (ASP015K)
JAK1 inhibitor	Oral	II	Itacitinib (INCB39110)
JAK1 inhibitor	Oral	II	Solcitinib (GSK2586184)
JAK1/2 inhibitor	Topical	II	Ruxolitinib (INCB018424)
JAK1/2 inhibitor	Oral	II	Baricitinib (LY3009104, INCB028050)
JAK1/2 inhibitor	Oral	II	PF-04965842
JAK1/3 inhibitor	Oral	III	Tofacitinib (CP-690550)
TYK2 inhibitor	Oral	II	PF-06826647
TYK2/JAK1 inhibitor	Oral	II	PF-06700841
ROCK2 inhibitor	Oral	II	Belumosudil (KD025)
S1P1 agonist	Oral	II	Ponesimod (ACT-128800)
S1P1 agonist	Oral	II	SCD-044
RoRγt antagonist	Oral	II	BI730357
RoRγt inverse agonist	Oral	I	AZD0284
RoRγt inverse agonist	Oral	II	AUR101
RoRγt inverse agonist	Topical	II	GSK2981278
VEGF antagonist	Topical	I	Pazopanib
TrkA inhibitor	Topical	II	CT327
TrkA inhibitor	Topical	II	Pegcantratinib (SNA-120)
Adenosine A3 receptor agonist	Oral	III	Piclidenoson (CF101)
NK1 receptor antagonist	Oral	III	Serlopitant
RIPK1 inhibitor	Oral	II	GSK2982772
NRF2 agonist	Oral	II	FP-187
NRF2 agonist	Oral	III	Almirall (LAS-41008)
STAT3 inhibitor	Topical	II	STA-21
PKC inhibitor	Oral	II	AEB071
Histamine H4 receptor antagonist	Oral	II	ZPL-3893787

预后得到明显提升。目前, 主要有4大类11种生物制剂被美国FDA批准用于银屑病治疗: TNF-α抑制剂 (英夫利昔单抗、阿达木单抗、依那西普和培塞利珠单抗)、IL-12/23抑制剂 (乌司奴单抗)、IL-17抑制剂 (司库奇尤单抗、依奇珠单抗和布罗达单抗) 和IL-23抑制剂 (古塞奇尤单抗、替拉珠单抗和瑞莎珠单抗)[3]。IL-17A/17F双效抑制剂比米珠单抗也被欧洲药品管理局 (EMA) 批准用于银屑病治疗。研究发现, 根据银屑病患者的遗传差异, 患者对于生物制剂的响应也有所不同。如HLA-C*06:02阳性的患者使用乌司奴单抗的疗效显著优于HLA-C*06:02阴性的患者, HLA-C*06:02有望成为乌司奴单抗治疗的生物标志物, 这有助于银屑病的个性化治疗[78]。

鉴于IL-17和IL-23/Th17轴在银屑病发病中的核心地位, 仍有一系列靶向这些细胞因子的生物制剂处于临床试验阶段。此外, IL-1β和IL-18是银屑病治疗的潜在靶点。阻断T细胞活化也成为新的治疗方向, 阿巴西普是人源CTLA-4细胞外功能区与IgG1 Fc段的融合蛋白, 通过阻断CD28-CD80/CD86共刺激信号通路抑制T细胞活化, 已被美国FDA批准用于银屑病关节炎, 并已开展治疗银屑病的II期临床试验。进入临床试验阶段的银屑病生物药如表4所示。

4　总结与展望

银屑病是一种复杂的多因素疾病, 至今仍无法治愈。其发生发展过程受多因素影响, 疾病进程中存在多种免疫细胞及细胞因子参与, 但目前的治疗药物只针对其中的部分环节, 因此疗效有限。优化联合用药或者开发多靶点药物或许能够作为银屑病治疗的新选择。此外, 近年发现的新机制, 如AhR信号通路和S1P信号通路, 它们在不同类型细胞中存在不同的作用机制及产生不同的效果, 这可能与受体具有多种亚型, 与不同亚型受体结合引起不同生物效应有关。对这些差异性进行深入挖掘, 一方面能够提升研发药物的靶向性, 另一方面可以借此发现更多能够用于银屑病治疗的靶点。

近年来, 生物制剂用于银屑病的治疗取得较大突破, 但其种类单一、价格较高, 且注射给药不方便患者使用, 因此丰富生物制剂种类、减少不良反应、扩大受

Table 4 Summary of biologics under clinical trials for psoriasis

Target	Stage	Name	Administration
IL-1R antagonist	II	Anakinra	s.c injection
IL-2R agonist	I	CC-92252	s.c injection
Anti-IL-12/23 p40 mAb	II	AK101	s.c injection
Anti-IL-12/23 p40 mAb	II	Briakinumab (ABT-874)	s.c injection
Anti-IL-12/23 p40 mAb	III	BAT2206	s.c injection
Anti-IL-17A mAb	I	CJM112	s.c injection
Anti-IL-17A mAb	II	AK111	s.c injection
Anti-IL-17A mAb	II	SHR-1314 (Vunakizumab)	s.c injection
Anti-IL-17A mAb	II	HB0017	s.c injection
Anti-IL-17A mAb	II	JS005-002	s.c injection
Anti-IL-17A mAb	III	Netakimab (BCD-085)	s.c injection
Anti-IL-17A mAb	III	SSGJ-608	s.c injection
Anti-IL-17A/F nanobody	I	MSB0010841	s.c injection
Anti-IL-23A/IL-23 p19 mAb	II	LY2525623	s.c/i.v injection
Anti-IL-23p19 mAb	III	Mirikizumab (LY3074828)	s.c injection
Anti-IL-36R mAb	III	Imsidolimab (ANB019)	s.c injection
Anti-IL-36R mAb	I	HB0034	s.c injection
Anti-CD25 mAb	II	Daclizumab	i.v injection
CTLA4 Ig	II	Abatacept	s.c/i.v injection
GM-CSF receptor antagonist	II	Namilumab (MT203)	s.c injection
Single-chain anti-TNF-α Ab	II	DXL105	Intra-dermal injection
PD-1 agonist	I	CC-90006	s.c injection
PD-1 agonist	I	Peresolimab (LY3462817)	s.c/i.v injection

益人群是未来发展的方向。此外, 为中、重度银屑病患者开发更安全、更有效和价格实惠的局部或系统治疗药物亦是需要解决攻克的难点。随着机制研究的不断深入, 银屑病的治疗靶点/通路不断丰富, 这为新药研发提供新的思路和启发。如何将表观遗传学靶点应用于银屑病药物研发中, 如何针对ncRNAs不稳定性设计合适的给药方式等。另外, 探究不同类型银屑病之间的差异有利于更加精准及个性化的治疗。相信随着研究的不断深入, 银屑病的病理机制会更加明确, 会有更多有针对性的治疗药物上市, 为患者提供更加有效的治疗方案。

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利益冲突: 作者声明无利益冲突。

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