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皮肤瘙痒的昼夜节律

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[摘 要] 瘙痒是皮肤病最典型和最重要的临床症状之一，也是皮肤病加重或复发的重要诱因之一。瘙痒严重影响患者的身心健康和生活质量，给患者、家庭和社会带来沉重的负担。瘙痒的发生和调控机制复杂，目前尚未阐明。临床研究显示在疥疮、慢性瘙痒、特应性皮炎和银屑病中均存在瘙痒夜间加重的情况，提示皮肤瘙痒可呈昼夜节律性改变。皮质醇、褪黑素、人体核心温度、细胞因子及前列腺素等因素是瘙痒昼夜节律的主要调控因素。一些生物钟基因如*BMAL1*、*CLOCK*、*PER*和*CRY*等，通过调节Janus激酶(Janus tyrosine kinase，JAK)-信号转导和转录激活因子(signal transducer and activator of transcription，STAT)通路与转录因子蛋白家族核因子κB(nuclear factor kappa-B，NF-κB)等信号通路，在瘙痒的昼夜节律的调节中扮演重要角色。然而生物钟基因对瘙痒昼夜节律调控的具体作用机制尚未完全阐明，进一步研究生物钟基因在瘙痒昼夜节律调控中的作用机制，将为阐明瘙痒的调控机制奠定基础，亦可为控制瘙痒和缓解皮肤病提供新的思路。

[关键词] 瘙痒；昼夜节律；生物钟；特异性皮炎

Circadian rhythm of cutaneous pruritus

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ABSTRACT One of the most common and significant symptoms for skin disorders is pruritus. Additionally, it serves as a significant catalyst for the exacerbation or reoccurrence of skin diseases. Pruritus seriously affects patients' physical and mental health, and even the quality of life. It brings a heavy burden to the patients, the families, even the whole society.

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The pathogenesis and regulation mechanisms for pruritus are complicated and have not yet been elucidated. Previous clinical studies have shown that itch worsens at night in scabies, chronic pruritus, atopic dermatitis, and psoriasis, suggesting that skin pruritus may change with circadian rhythm. Cortisol, melatonin, core temperature, cytokines, and prostaglandins are the main regulatory factors of the circadian rhythm of pruritus. Recent studies have shown that some CLOCK genes, such as *BMAL1*, *CLOCK*, *PER*, and *CRY*, play an important role in the regulation of the circadian rhythm of pruritus by regulating the Janus tyrosine kinase (JAK)-signal transducer and activator of transcription (STAT) and nuclear factor kappa-B (NF-κB) signaling pathways. However, the mechanisms for circadian clock genes in regulation of circadian rhythm of pruritus have not been fully elucidated. Further studies on the mechanism of circadian clock genes in the regulation of circadian rhythm of pruritus will lay a foundation for elucidating the regulatory mechanisms for pruritus, and also provide new ideas for the control of pruritus and the alleviation of skin diseases.

KEY WORDS　pruritus; circadian rhythm; biological clock; atopic dermatitis

瘙痒(pruritus)是一类在皮肤病和全身性疾病中十分常见的症状，被定义为一种需要抓挠的、不愉快的感觉。瘙痒根据发作持续时间的长短可分为急性瘙痒和慢性瘙痒；也可以根据发作来源的不同，分为全身性疾病瘙痒(如尿毒症、胆汁淤积等引起的瘙痒)和皮肤病性瘙痒(如特异性皮炎和银屑病引起的瘙痒)[1-2]。在临床上，皮肤引起的不自主的搔抓常引起瘙痒部位的刺痛感和烧灼感，给患者带来不适感。皮肤瘙痒是皮肤病最常见的临床表现之一，瘙痒搔抓常导致皮肤屏障受损，从而加重或者导致皮肤病的复发，因此瘙痒也是皮肤病加重或复发的常见诱因之一[1]。此外，皮肤瘙痒常引起患者睡眠障碍，严重影响患者的生活质量，导致心理疾病甚至自杀，给患者家庭和社会带来沉重的负担[1, 3-4]。因此研究皮肤瘙痒的发病机制，从而控制皮肤瘙痒一直是临床研究的焦点。

昼夜节律又称生物钟，是指在生理或生物学行为上所表现的以约24 h为周期的生物节律。在哺乳动物中，位于下丘脑的视交叉上核(suprachiasmatic nucleus，SCN)被广泛认为是协调整个身体时钟的昼夜节律振荡器，由视网膜下丘脑束传来的光信息通过SCN承载的昼夜起搏器达到与生物节律的同步[5-7]。机体的睡眠、体内激素水平、新陈代谢及食欲等众多的生理过程离不开生物钟的调控，而免疫、内分泌、消化、心血管等方面疾病的发生也受到生物钟的调控[8-12]，皮肤温度、pH值、渗透性和经皮失水量(transepidermal water loss，TEWL)等的调节，以及皮肤相关疾病如皮肤癌、皮肤瘙痒的发生与生物钟的调控密切相关[13-15]。皮肤瘙痒具有显著的昼夜节律，但其具体机制不明，进一步研究并揭示皮肤瘙痒昼夜节律的调控机制将为控制瘙痒提供重要的线索。笔者对已有的皮肤瘙痒昼夜节律的研究进行综述，以期为瘙痒昼夜节律的研究提供思路。

1 皮肤瘙痒昼夜节律的临床研究

近年来，皮肤病如疥疮、慢性瘙痒、特异性皮炎(atopic dermatitis，AD)及银屑病等引起瘙痒的临床研究[16-19]显示瘙痒常在夜间加重；肝、肾疾病也会引起皮肤瘙痒，且傍晚或夜间会加重[20-23]。皮肤瘙痒具有明显的昼夜节律，具体研究结果和昼夜节律特征总结见表1。

2 瘙痒昼夜节律的主要调控因素

2.1 皮质醇

下丘脑-垂体轴是人体昼夜节律调控的重要因素。皮质醇是由肾上腺皮质产生的类固醇，具有抗炎作用，其在早晨分泌增加，而夜晚分泌下降，具有典型的24 h昼夜节律。除了肾上腺分泌的皮质醇以外，应激暴露的角质形成细胞促肾上腺皮质激素释放激素分泌增高，可使皮肤角质形成细胞和成纤维细胞分泌促肾上腺皮质激素，进而导致皮质醇和皮质酮的分泌[24]。血清皮质类固醇水平通常在晚上处于低

谷，这意味着该激素的抗炎作用在这段时间内最弱，可能会加剧炎症性皮肤病。因此，许多学者认为夜间AD引发瘙痒强度的增加与皮质醇的节律密切相关。

表1 皮肤瘙痒昼夜节律的临床研究

Table 1 Clinical study on circadian rhythm of cutaneous pruritus

瘙痒类型	研究群体	瘙痒的临床表现	参考文献
银屑病	101例广泛性银屑病患者	84%的患者出现全身性瘙痒，77%的患者表示每天都会出现瘙痒，并指出瘙痒主要在夜晚发生	[16]
慢性瘙痒	302例来自墨西哥西班牙裔的老年人(120例来自疗养院，182例来自老年门诊)	约88%的患者报告瘙痒每天都会发生，并且65%的患者报告瘙痒在夜间更加严重	[17]
疥疮	193例患疥疮而住院的患者	181例(93.8%)患者报告瘙痒在夜间更加严重	[18]
特异性皮炎	102例已知患有特异性皮炎的中国患者(其中有100例患者填写了问卷)	87%的患者每天有瘙痒，瘙痒的持续时间较长并且遍及全身；65%的患者表示瘙痒在夜间更加频繁	[19]
特应性皮炎	240例未成年AD患者(60例婴儿、120例儿童和60例青少年)	患者均报告最严重的瘙痒发生在工作日的晚上7:00和周末的晚上8:00	[20]
肝病相关瘙痒	74例肝病相关瘙痒患者，其中有17例(23%)被认定为瘙痒	瘙痒评分在一天的前半段相对较低(接近于零)，然后在下午/傍晚时分增加	[21]
慢性肾病相关瘙痒	103例慢性血液透析患者	84%的患者报告每天出现瘙痒症状，且夜间瘙痒相比白天更严重	[22]
丙型肝炎相关瘙痒	1 614例HCV感染患者	瘙痒通常是在全身范围内发生的，早期主要发生在脚底和手掌，夜间和晚上瘙痒最严重	[23]

AD：特异性皮炎；HCV：丙型肝炎病毒。

2.2 褪黑素

褪黑素主要由松果体分泌，其他组织如皮肤组织也可以分泌褪黑素。褪黑素的分泌也具有昼夜节律，在夜晚(黑暗)开始不久后增加分泌，在凌晨1:00–4:00其血清水平达到峰值。规律分泌的褪黑素通过影响其受体，驱动靶组织结构中的昼夜节律，如腺垂体或同步外周振荡器，如胎儿肾上腺，还有许多其他组织外周组织。褪黑素的这种分泌节律还可以有效地调节睡眠-觉醒周期，褪黑素浓度在黑暗之前随着光线的消退而上升，在黑暗中达到峰值，并在暴露于光线时下降以促进清醒，褪黑素分泌节律还在SCN中起作用，以减弱生物钟的觉醒促进信号，从而促进睡眠，褪黑素的分泌异常与睡眠障碍的出现以及抑郁症的发展有关，所以褪黑素常被认为是昼夜节律的主要调控因素[25-26]。褪黑素具有较强的抗炎和抗氧化能力，可能与AD的慢性皮肤炎症和睡眠障碍直接相关，但是针对AD患者体内褪黑素水平的研究[27]结果差异较大。早在1988年，有研究[28]每隔2 h检测18例重度AD患者血清褪黑素的水平，结果显示患者体内的褪黑素含量明显降低，其褪黑素分泌的昼夜节律有明显的削减和消除。褪黑素能够刺激免疫细胞产生肿瘤坏死因子α(tumor necrosis factor-α，TNF-α)、白细胞介素(interleukin，IL)-6、IL-12等抗炎因子来增强细胞的抗炎能力，同时也可以增加细胞中C反应蛋白的含量从而促进抗炎过程的发生[29-30]。褪黑素亦能够直接作用于肥大细胞，抑制其增殖，同时褪黑素在炎症反应时还能通过影响T细胞活性，抑制Th17细胞释放相应细胞因子[31-34]。有研究[35]采用褪黑素进行干预用来调节昼夜节律，因此一些学者也提议用褪黑素来治疗夜间瘙痒。综上，褪黑素水平的夜间波动与AD的瘙痒密切相关。

2.3 人体核心温度

人体的核心温度是由位于人体脑部下丘脑内部的体温调节中枢所设定的。核心温度的变化具有显著的昼夜节律，在傍晚达到峰值而在清晨降至最低。人体核心温度与皮肤温度的变化呈现出相反的模式，即核心温度的降低总是伴随着皮肤温度的升高，两者具有相反的节律。研究[36-37]发现：在非快速眼动(non-rapid eye movement，NREM)睡眠阶段，随着下丘脑的体温调节中枢温度设定点降低，人体的核心温度随之降低，从而导致外周皮肤温度升高，而瘙痒强度随外周皮肤温度的升高而增强。因此在

NREM睡眠阶段，核心温度的降低、皮肤温度的升高可诱导瘙痒发生。

2.4 细胞因子

IL-2、IL-8能够诱导瘙痒[27]。IL-2被认为是诱导慢性瘙痒的一种介质。研究[38]发现，与未出现瘙痒症状的银屑病患者相比，患有瘙痒的银屑病患者病变的皮肤组织中IL-2免疫反应性淋巴细胞显著增加，证实了促炎因子IL-2在诱导银屑病瘙痒中的作用。另有研究[39]发现IL-2的含量总是在夜间增加。因此IL-2也被认为是夜间瘙痒的诱因。IL-8受核心生物钟基因CLOCK(circadian locomotor output cycles kaput)的负向调控，在紫外线辐射诱导的昼夜节律紊乱中，CLOCK表达下调而IL-8表达上调，从而诱导皮肤炎症和瘙痒[40]，提示IL-8参与了瘙痒昼夜节律的调控。

2.5 前列腺素

皮肤屏障功能障碍是AD发病的关键因素之一，AD患者中常存在皮肤屏障功能的紊乱[41-42]。前列腺素(prostaglandin，PG)D2是由前列腺分泌的前列腺素之一，具有修复皮肤屏障损伤的功能。小鼠体内PGD2的含量出现昼夜波动，在白天达到最高，在夜间降至最低。研究[43]表明PGD2和PGE2通过特异性前列腺素受体加速机械抓挠引起的皮肤屏障破坏的恢复过程。因此有学者[44]提出PG的昼夜节律可能在夜间瘙痒加重的患者中被打乱。

3 生物钟基因对于瘙痒的调控

在分子水平上，生物钟由核心生物钟基因调控，主要包括*CLOCK*、*BMAL1*、*PER*、*CRY*、*RORA*和核受体亚家族1D组成员1(nuclear receptor subfamily 1 group D member 1，*NR1D1*)。昼夜节律由*BMAL1*/*CLOCK*复合体驱动的正反馈回路和*PER*/*CRY*复合体介导的负反馈回路调控，它们对于整个生物体维持日常节律及调节细胞的周期具有核心作用[5, 39]。

3.1 JAK/STAT通路

AD的发生与Janus激酶(Janus tyrosine kinase，JAK)-信号转导和转录激活因子(signal transducer and activator of transcription，STAT)通路的作用密不可分[46]。2种经过活化后的JAK蛋白经过相应的组合后促进STAT蛋白的磷酸化进程并诱导STAT蛋白的二聚化，STAT蛋白经过二聚化后异位到细胞核上影响相关基因的表达[45]，从而诱导细胞中IL-4、IL-31因子的产生。而IL-4、IL-31在AD的发病中起至关重要的作用[46]，因此JAK/STAT通路主要通过诱导IL-4、IL-31的产生来介导AD瘙痒的发生。JAK/STAT通路发挥作用的机制受到生物钟的调控。JAK/STAT通路是IL-4诱导时钟基因*PER2*表达的重要媒介，IL-4能够通过激活JAK/STAT信号通路和HaCaT角质形成细胞中*PER3*启动子的活性来增强*PER2*表达，同时由IL-2介导JAK/STAT通路引起的*PER3*表达的上升会引起体内多种促炎因子的释放从而助于AD的发生[47-48]。研究[49]发现，在*Cry*缺失的小鼠体内，STAT蛋白的磷酸化程度出现了明显的下降，说明*Cry*对于JAK/STAT通路起调控作用。另一相关的研究[50]表明：JAK/STAT的相关表达产物在果蝇体内呈现出昼夜循环的表达，STAT92E的含量会在傍晚达到峰值，并且循环会一直持续到第2天。上述研究表明*Cry*基因可以通过调控JAK/STAT通路从而诱导AD的发生。

3.2 NF-κB通路

*NF-κB*是核心转录因子之一，在诱导细胞促炎因子IL-6和IL-1β的表达方面起关键作用[51]。IκBa的磷酸化对于*NF-κB*因子的激活具有重要作用：*NF-κB*因子激活后转移到细胞核中对靶基因的相关表达进行调控[52]，从而诱导促炎因子IL-6和IL-1β的表达。慢性肾病患者最常见的临床表现是瘙痒以及血液中磷酸钙(calcium acid phosphate，Cap)含量的升高。Cap诱导AD瘙痒发生的通路离不开IL-6的参与：对某患者群体体内的IL-6阳性的染色体进行分析，发现患者非瘙痒皮肤中的IL-6含量远低于瘙痒皮肤内IL-6的含量；在进行血液透析的患者中，血液中IL-6含量竟是正常人的5倍之多[53]。这些研究说明IL-6在诱导慢性肾病相关瘙痒中起关键作用。活性氧(reactive oxygen species，ROS)在分子层面能够抑制IκBa的磷酸化从而抑制*NF-κB*发挥作用。相关研究[54]发现ROS与生物钟间存在联系。该研究对体内*Bmal1*缺失以及*Bmal1*正常的2组小鼠的真皮与表皮进行分析，结果发现，在*Bmal1*缺失的小鼠体内，ROS的含量更高，证实ROS含量的变化是受时钟基因调控[54]。因此*BMAL1*调控ROS含量的过程影响了*NF-κB*诱导IL-6因子的生物学过程，这很可能诱导了AD的发生。

3.3 水通道蛋白3

研究[55]表明：水通道蛋白3(aquaporin 3，AQP3)在皮肤水合作用中发挥的效应可能与AD的发生相关联。在AD病变的人类皮肤组织样本中，与AQP3相关基因的转录以及蛋白质的表达显著增加，并且在病变皮肤组织中，对于AQP3形成具有强诱导作用的CCL17也呈高表达，这表明AQP3对于AD病变皮肤表皮增生起作用。AQP3在正常小鼠皮肤中的表达被

检测出具有明显的昼夜节律，而在*CLOCK*基因发生突变的小鼠体内，AQP3急剧减少。研究[56]通过荧光素酶报告基因分析发现野生型小鼠表皮的mAqp3基因转录被d位点结合蛋白(一种时钟基因)激活，表明小鼠AQP3的昼夜节律受到时钟基因的严格调控；同时，他们发现人类同源物hAQP3在人角质形成细胞(HaCaT)细胞中也表现出显著的节律，与含有50%血清的培养基同步；人体内AQP3发挥的相关作用受到内源性*CLOCK/BMAL1*时钟基因异二聚体的调节。因此，生物钟基因可能通过抑制AQP3的转录和表达参与对AD的调控。

4 结 语

作为皮肤疾病最常见的临床症状——瘙痒，常引起剧烈的搔抓，不仅破坏皮肤屏障，引起皮肤疾病的加重和复发，还严重影响患者的生活质量和身心健康，一直是临床治疗的难题。控制瘙痒对缓解皮肤病具有至关重要的意义。一些皮肤病如特应性皮炎、银屑病等的瘙痒常在夜间加重，呈昼夜节律性改变，这与褪黑素、皮质醇、皮肤屏障、人体核心温度和细胞因子等调控因素密切相关。目前，关于通过调控昼夜节律治疗皮肤病的研究较少。Chang等[57]曾使用褪黑素治疗1~18岁的AD患者，与对照组相比，服用褪黑素4周后，AD患者的疾病严重程度和睡眠质量得到改善。JAK/STAT信号通路与多个生物钟核心基因存在密切关系，近年来多个JAK抑制剂也应用于AD的临床治疗中，且具有不错的疗效[58]；但研究多集中在其对炎症通路的调控，鲜有此通路与生物钟基因间的调控研究。研究生物钟基因在瘙痒昼夜节律中的作用和调控机制，将为阐明瘙痒的发生和调控机制提供重要线索，也将为控制瘙痒、缓解皮肤病奠定基础，因此，这仍将是未来皮肤病领域一个非常重要的研究方向。

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