

炎症性肠病中的昼夜节律: 从生理基础到时间医学应用

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摘要 炎症性肠病(inflammatory bowel disease, IBD)是一种以胃肠道慢性炎症为特征的易复发性疾病, 其临床病理特征主要表现为肠道黏膜的持续性炎症损伤和修复异常, 主要分为克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC)两种临床亚型. 最新研究表明, 昼夜节律紊乱(circadian rhythm disorder, CRD)与IBD的发病机制、疾病进展以及治疗效果密切相关. 本文系统阐述了肠道生理学中的昼夜节律、IBD患者的昼夜节律表达模式, 以及昼夜节律对IBD肠道中微生物菌群、肠道黏膜屏障及免疫系统的调控机制. 此外, 基于IBD症状、炎症活动度及药物疗效均呈现昼夜依赖性, 本文还进一步展望了基于节律调节的时间医学(chrono medicine)策略(包括昼夜节律调节药物、时间药理学、择时给药、限时禁食等)在IBD治疗中的潜在应用前景, 为优化临床实践提供理论支持和治疗思路.

关键词 炎症性肠病, 昼夜节律, 肠道菌群, 肠道免疫, 时间医学, 择时治疗

炎症性肠病(inflammatory bowel disease, IBD)是一种以胃肠道慢性炎症为特征的易复发疾病, 主要划分为克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC). 进入21世纪, 西方国家IBD的发病率趋向稳定, 然而在低收入及中等收入国家, 发病率正急剧升高^[1-3]. 截至2021年, 我国IBD患者的总人数为168077人, 新增的病例数量为24941例, 有5640例死亡病例^[4]. 中国被列为全球IBD“发病率加速期”(阶段2)的典型代表^[5], 东亚地区年均增长率居全球首位, 预计2035年新发病例上升到41000多例, 死亡病例预计达到6500多例^[6]. 当前, IBD治疗主要借助调节免疫系统以抑制炎症反应^[7], 但现有的治疗措施经常伴有严重并发

症风险以及高昂的医疗费用, 让患者及其家庭背负了明显的负担.

昼夜节律(circadian rhythm)源自拉丁语“circa”(意为“大约”)和“diem”(意为“天”), 合起来即“大约一天”, 形象描述了生物钟接近24 h的周期性特征. 昼夜节律是一套复杂的生物钟系统, 包括前下丘脑的视交叉上核(suprachiasmatic nucleus, SCN)构成的中枢生物钟, 以及其他外周器官组织构成的外周生物钟系统, 共同调控着机体的多种生理功能^[8]. 肠道作为重要的外周生物钟系统器官之一, 其功能活动具有显著的昼夜节律性特点^[9]. 而该节律的紊乱, 也成为了目前IBD相关研究中广泛关注的致病因素和研究热点. 为此, 本文将

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系统阐述昼夜节律的调控机制及其如何影响IBD的发生与发展,旨在为IBD的管理、预防及治疗提供科学依据。

1 昼夜节律与IBD

1.1 昼夜节律紊乱诱导IBD

昼夜节律紊乱(circadian rhythm disorder, CRD)的诱发因素复杂多样,现代社会普遍存在夜间光照暴露、社交时差、熬夜、失眠、进食时间不固定等因素,通过干扰SCN或外周生物钟的同步性,导致节律失调^[10,11]。CRD在诱发IBD中的情况较为常见,且与疾病活动状态密切相关。Weintraub等人^[12]在新诊断的IBD患者的炎症与非炎症的肠黏膜组织中发现,核心生物钟分子,如*Bmal1*(brain and muscle arnt-like 1)、*Clock*(circadian locomotor output cycles kaput)、*Per1/2*(period circadian regulator 1/2)、*Cry1/2*(cryptochrome circadian regulator 1/2)等的表达均显著降低,且与炎症标志物(C反应蛋白、钙卫蛋白)升高相关。该异常表达不仅存在于肠道局部,还表现为外周血白细胞中生物钟基因的系统性下调,表明昼夜节律紊乱是IBD发病的早期表现。Ananthakrishnan等人^[13]对230例UC和191例CD展开研究发现,与每天睡眠7~8 h的人群相比,每天睡眠小于6 h者UC患病风险升高51%,而睡眠大于9 h者患病风险翻倍,但都与CD患病风险无关。此外,IBD患者的疾病活动度增加与CRD相关。Ananthakrishnan等人^[14]通过3173名IBD患者的数据分析发现,在1291名CD处于缓解状态的患者中,睡眠受损的患者在6个月时活动性疾病的风险增加了2倍,但在UC患者中没有观察到影响。Swanson等人^[15]招纳了5名UC受试者从中分离培养结肠类器官。凭借3天的明暗周期交替诱导CRD,进而造成紧密连接蛋白表达下降,由此破坏结肠屏障的整体完整性。Zhang等人^[16]利用*Bmal1*表达下调CRD小鼠模型研究证实,CRD对DSS诱导的结肠炎更敏感并且肠道屏障功能受损更严重,而将*Bmal1*过表达能够可逆转损伤。这些研究结果均一致表明,CRD是诱发IBD并使病情恶化的一个重要风险因素。

1.2 IBD发生发展的节律性

IBD的发病风险与季节变化以及地理纬度存在一定关联。在冬季或春季部分地区会有IBD发病率上升、患者症状加重的现象,其疾病的活动度受太阳辐射相

关联的维生素D水平、不同遗传背景、环境及饮食习惯等因素所影响^[17-21]。临床上,IBD的主要症状包括腹痛、腹泻及便血等方面^[22],其发作频率及严重程度也呈现出典型的昼夜节律波动规律。肠道内压、环形肌收缩力以及排便活动皆呈现出显著的昼夜节律性,表现为昼间增强、夜间减弱^[23-25]。研究表明,IBD患者往往会出现早晨腹泻加重的情形,此现象和皮质醇节律性分泌在清晨出现峰值以及结肠运动的昼夜高峰密切相关^[26,27]。IBD诱发的腹痛多在夜间发作,其发病机制主要与迷走神经兴奋性上升引起内脏超敏反应,及炎症因子释放量增加相关^[28,29]。心理压力、不规律进食与生活方式等因素同样会影响IBD患者症状表现,并在特定阶段使症状进一步加剧^[30,31]。总之,IBD患者症状一般呈现出节律性特性,而这种节律性会被神经内分泌激素、炎症因子以及外界环境等多种因素一同影响。

2 昼夜节律调控IBD的分子机制

2.1 昼夜节律分子通路

昼夜节律是由生物钟分子的表达产物通过自我调控循环(包括合成、积累和降解)所驱动的周期性生理节律系统。研究表明,哺乳动物的昼夜节律主要由以三重互锁的转录-翻译反馈环(three interlocked transcription-translation feedback loops)协同调控(图1): (1) 核心正负反馈通路。核心生物钟分子*Clock*和*Bmal1*编码的蛋白可形成异源二聚体,结合下游靶基因(如*period*(*Per1/2/3*)和*cryptochrome*(*Cry1/2*))启动子区域的E-box元件上来激活靶基因的转录,随着*Per*和*Cry*基因不断转录和翻译,其蛋白逐渐积累并进入细胞核中,能够抑制CLOCK-BMAL1复合物的活性,进而减少其基因的转录。当PER/CRY复合物在细胞核内受酪蛋白激酶1 ϵ (casein kinase 1/cell kinase 1 ϵ , CK1 ϵ)等激酶催化的磷酸化水平达到阈值时^[32], β -转导素重复序列包含蛋白(beta-transducin repeats-containing proteins, β -Trcp)识别磷酸化PER并介导其泛素化降解^[33,34]。F-box富含亮氨酸重复蛋白3(F-box and leucine-rich repeat protein 3, FBXL3)在细胞核中识别磷酸化CRY1/2并启动泛素化级联反应使其降解^[35];而在胞质内,F-box富含亮氨酸重复蛋白21(F-box and leucine rich repeat protein 21, FBXL21)则介导CRY部分非降解型泛素化,延缓其入核并缓冲降解速率。这种平衡使CRY的降解滞后从而

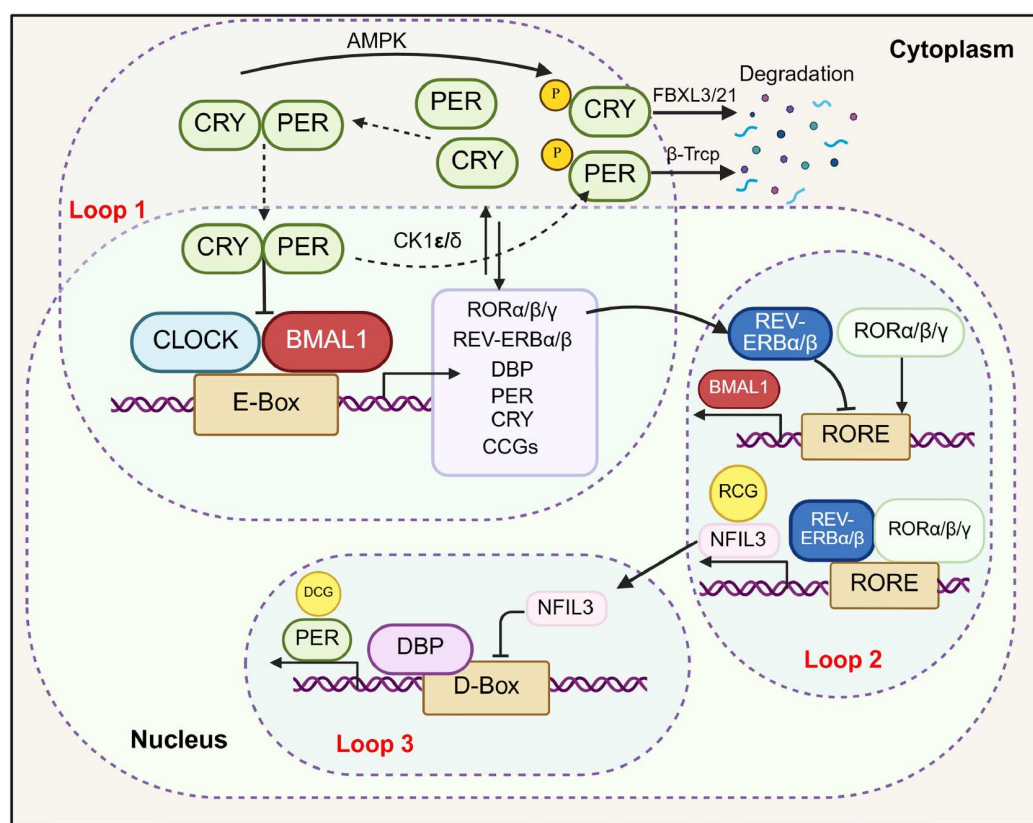


图1 生物钟的分子机制。(1) 核心环路(Loop 1): CLOCK/BMAL1异源二聚体与E-BOX结合激活下游基因, CRY、PER蛋白积累后入核抑制其活性。(2) 辅助环路(Loop 2): CLOCK/BMAL1激活ROR和REV-ERB, 其产物分别通过RORE元件激活或抑制BMAL1表达。(3) 次级环路(Loop 3): CLOCK/BMAL1诱导DBP激活D-box元件, 而NFIL3竞争性结合D-box起抑制作用。图片由BioRender.com制作

Figure 1 Molecular mechanisms of the biological clock. (1) Core circuit (Loop 1): the CLOCK/BMAL1 heterodimer binds to the E-BOX to activate downstream genes; CRY and PER proteins accumulate and enter the nucleus to inhibit their activity. (2) Auxiliary circuit (Loop 2): CLOCK/BMAL1 activates ROR and REV-ERB, whose products activate or inhibit BMAL1 expression through the RORE element, respectively. (3) Secondary circuit (Loop 3): CLOCK/BMAL1 induces DBP to activate the D-box element, while NFIL3 competitively binds to the D-box to exert an inhibitory effect. Created with BioRender.com

抑制CLOCK/BMAL1转录活性的时间^[36]。(2) RORE调控环。BMAL1-CLOCK复合物还可以激活核受体视黄酸受体相关孤儿受体 $\alpha/\beta/\gamma$ (retinoic acid receptor-related orphan receptor $\alpha/\beta/\gamma$, ROR $\alpha/\beta/\gamma$)和REV-ERB α/β (也称为核受体亚家族1组D成员1/2(nuclear receptor subfamily 1, group D member1/2, NR1D1/NR1D2))的转录。其中, Rev-erba/ β 能够结合到*Bmal1*基因启动子区域的RORE元件上, 抑制BMAL1的转录。相反ROR $\alpha/\beta/\gamma$ 是正向调节因子, 能够激活BMAL1的转录。这种反馈机制进一步调节CLOCK-BMAL1复合物的活性^[37,38]。(3) D-box调控环。BMAL1-CLOCK复合物还可以诱导*Dbp*(D-site binding protein)基因的表达, DBP可以与D-box结合从而激活下游*Per*基因的表达。然而, NFIL3(nuclear factor, interleukin 3 regulated)作为ROR的靶基因产物, 能竞争

性结合D-box, 抑制相关基因表达^[39]。总之, 这些通路相互交织, 形成约24 h的转录-翻译振荡网络, 从而精确调控机体的代谢与生理节律。

2.2 昼夜节律调控肠道菌群

即便肠道菌群并非直接受光照影响, 但宿主昼夜节律可调控肠道微生物的数量、功能以及定植行为等出现昼夜节律性的变动^[40]。研究表明, 超过20%的小鼠及大约10%人类的肠道共生菌群丰度受生物钟分子调控出现昼夜节律性的变动, 且与宿主的行为活动呈现一致性^[41,42]。小鼠粪便里的细菌数量在夜间23点前后达到顶峰, 到早上7点的时候降至最低点, 拟杆菌门的平均丰度在夜间23点以及上午11点较高, 而厚壁菌门的平均丰度在凌晨3点和上午7点达到最高值^[43]。此外,

跟白天情况不同,夜间肠道菌群与肠道黏膜上皮细胞的空间距离更为接近。这种改变使得肠道上皮细胞周期性地接触不同种类细菌及其代谢产物^[44]。总而言之,肠道菌群展现出节律性的变化属性,对维持宿主日常生理功能和整体健康状况起着极为关键的作用。

宿主对肠道菌群昼夜节律的调控,主要途径有以下两个方面:(1) 宿主生物钟分子的直接调控。核心生物钟分子*Clock*突变引发的CRD打破了肠道微生物的稳态,在饮食应激等因素的作用下,该效应会被进一步增强^[45]。Altaha等人^[46]敲除小鼠SCN中的*Bmal1*从而破坏中枢昼夜节律功能,发现肠道菌群中厚壁菌门(Firmicutes)和拟杆菌门(Bacteroidetes)等有益菌数量丰度节律性完全消失,与炎症相关的扭链瘤胃球菌(*Ruminococcus*)丰度显著增加,而抗炎菌属(如普氏栖粪杆菌)减少。Yang等人^[47]利用CRISPR/Cas9技术敲除食蟹猴外周肠道*Bmal1*基因,与*Bmal1*敲除小鼠肠道微生物昼夜节律性完全丧失不同,BMAL1敲除食蟹猴的肠道微生物呈现异常节律模式,检测到普雷沃氏菌属(*Prevotella*)和拟普雷沃氏菌属(*Alloprevotella*)在夜间显著富集。该现象与*Bmal1*基因直接调控的过氧化氢(H_2O_2)节律性相关。在*Per1/Per2*双敲除的小鼠中,也观察到肠道菌群(如Bacteroidetes)的节律性波动几乎完全丧失,并且大部分功能(如维生素代谢、分泌等)也失去了原有的昼夜节律变化规律^[48]。此外,雌性小鼠肠道菌群丰度表现出更加显著的昼夜振荡,且易受生物钟紊乱的影响。在*Bmal1*基因缺失条件下,雄性小鼠细菌类群显著下降;而雌性小鼠除菌群相对丰度减少外,BMAL1的敲除还引起了不同的变化模式,蓝细菌门(Cyanobacteriota)、解糖微小寄生菌(Saccharibacteria)及软壁菌门(Tenericutes)的变化方向与雄性相反^[43]。其原因在于除生物钟分子直接驱动肠道菌群的昼夜节律外,还与性别因素存在交互作用。雌激素相较于睾酮具有较弱的生物钟调节作用^[49],并且SCN中的雌激素受体主要位于星形胶质细胞;相反,雄激素受体位于SCN核心VIP神经元,主要调节昼夜节律相位而非振幅^[50]。因此雌性小鼠的肠道菌群更易受CRD的影响。(2) 饮食节律的间接调控。饮食的时间影响,包括合适进食、用餐时间以及频率,会对肠道微生物的组成与功能造成改变^[51]。规律饮食可诱导约15%的共生细菌分类单位呈现出日内波动,并且能够增加微生物的丰度^[52]。相反,Ni等人^[53]发现大鼠不规律的进食(晚餐时间)导致肠道等外周组织多个关键节律基因(包括*Per2*、*Cry1*和*Rev-erba*等)的

表达峰值时间向后推移,并且微生物 α 多样性指数显著降低且昼夜节律振荡的消失;与此同时,变形菌门(Proteobacteria)等机会致病菌相对丰度升高,而具有抗炎作用的共生菌则减少。小鼠定时喂养实验(仅在光照阶段或仅在黑暗阶段获得食物)表明,在改变喂食时间后菌群操作分类单元(operational taxonomic units, OTUs)昼夜节律振荡表现出约12 h的相移,这表明通过饮食时间能够控制微生物群昼夜节律^[48]。Heddes等人^[54]通过饥饿小鼠48 h后发现,微生物群总体多样性失去昼夜节律,但占主导地位的Firmicutes与Bacteroidetes仍维持振荡节律。规律进食能让约16%的OTUs获得或增强节律性,但特异性敲除小鼠肠上皮细胞(intestinal epithelial cell, IEC)中*Bmal1*基因后,出现菌群(包括Firmicutes与Bacteroidetes)丰度节律性完全消失的现象,并且菌群整体功能(如SCFA产生、氨基酸代谢)也丧失节律。这表明食物只是微生物昼夜节律的调节因素,而IEC中的生物钟分子才是主要驱动因素。综上所述,宿主的生物钟分子和规律饮食通过调控肠道微生物的昼夜节律,进而同步影响肠道微生物数量、组成及功能的昼夜变化,一旦这种平衡被打破,可能会破坏肠道的微生物稳态,进而加速慢性炎症产生。

2.3 昼夜节律调控肠道黏膜屏障

IEC是肠壁的主要细胞类型,它们之间紧密连续排列,形成了一道物理屏障^[55,56]。昼夜节律存在于胃肠道黏膜屏障,参与胃肠道稳定性和肠道细胞增殖分化。有研究报道,肠黏膜细胞更新周期具有节律性变化,肠黏膜细胞增殖周期阶段中S期的最高表达率在夜间,而有丝分裂的活性最高于清晨,最低于傍晚。除此之外,与其相关的周期蛋白也表现出节律性变化^[57]。IEC还可以通过黏液和抗菌肽来增强肠道屏障功能,其中抗菌肽的表达具有昼夜节律特征,每天夜间21点达到峰值,在其他时间内,其相对表达值较低^[58]。

肠黏膜屏障作为抵御微生物入侵的首要屏障,其损伤是诱发IBD以及引发肠外脏器功能失调的主要原因。在IBD活动期患者中,往往出现IEC增殖能力降低、肠黏液分泌减少及通透性升高等现象^[7,59]。Taleb等人发现IEC的节律性受*Bmal1*的调节,在葡聚糖硫酸钠(dextran sulfate sodium salt, DSS)诱导肠道屏障受损的小鼠模型中,*Bmal1*的缺失会大大减少其肠道的细胞增殖能力^[60]。Summa等人^[61]在慢性酒精摄入诱导产生的肠道屏障高通透性的动物模型中,节律基因的失调或

者缺失会导致小鼠肠上皮屏障通透性增加. Kyoko等人^[62]进一步验证这一观点, 在*Clock*突变型小鼠结肠上皮中发现*Occludin*及*Claudin-1*的mRNA和蛋白表达失去昼夜节律性波动, 同时也出现了肠道黏膜通透性升高的情况. 在正常生理过程中, CLOCK-BMAL1异二聚体能够与*Occludin*和*Claudin-1*基因启动子上特定的E-box位点结合而表现出明显的昼夜差异. 具体而言, 在小鼠模型(夜行性活动)中*Clock/Bmal1*基因对二者基因E-box的结合效率在授时因子时间(zeitgeber time, ZT)4时最高, 其对*Occludin*基因E-box的结合率相较于ZT16时昼夜差异表达降低约60%~70%; 而对*Claudin-1*基因E-box的结合率变化幅度较小, 昼夜差异仅约40%~50%. 另外, 小鼠结肠和回肠中*Per1/2*基因缺失可以导致IEC、潘氏细胞、杯状细胞、溶菌酶及黏蛋白的转录物和蛋白质水平大幅降低, 从而造成保护性屏障的分泌上皮细胞的选择性损失^[63]. 总之, 昼夜节律是调控肠黏膜屏障动态变化的关键因素, 其紊乱会引发肠漏现象, 进而增加有害细菌或内毒素易位的风险, 最终引起肠道免疫细胞的异常激活, 加重肠道炎症的发生态势.

2.4 昼夜节律调控肠道免疫系统

在人与动物体内, 肠道是最大的外周淋巴器官, 约三分之二的免疫组织集中分布于肠道系统. 肠道免疫系统与昼夜节律之间存在着密切的相互作用, 这种调控关系体现在诸多层面: 生物钟分子对细胞信号通路的转录和翻译、免疫细胞的活化、增殖和迁移实施调控.

2.4.1 昼夜节律调控先天性免疫系统

巨噬细胞为肠道关键的先天免疫细胞, 大约8.4%的巨噬细胞基因表达呈现出昼夜节律性^[64]. 巨噬细胞依靠分泌细胞因子和趋化因子参与到肠道炎症反应中, 由巨噬细胞生成的NADPH氧化酶(NADPH oxidase 2, NOX2)与超氧化物歧化酶(superoxide dismutase, SOD)会受到BMAL1/CLOCK二聚体的精确调控, 这使得活性氧(reactive oxygen species, ROS)的生成呈现出节律性起伏^[65]. *Bmal1*的缺失会引起巨噬细胞的节律性浸润出现紊乱, 从而加剧炎症反应^[66]. *Rev-erba*通过负向调控趋化因子配体2(C C motif ligand 2, CCL2)的表达, 进而抑制巨噬细胞介导的促炎反应^[67]. 当这种表达被去除时, 会引起小鼠NLRP3炎性小体的激活, 使其在DSS诱导的结肠炎方面更敏感^[68]. 自然杀伤细胞

(natural killer cell, NK)通过细胞毒作用及促炎因子的分泌, 参与到IBD早期黏膜损伤中. NK细胞的生物钟分子表达呈现出昼夜节律性, 它释放的细胞溶解因子和细胞因子(IFN- γ 和TNF- α)的mRNA及蛋白表达也呈现昼夜节律性, 并且这些表达的峰值和生物钟分子联系紧密^[69]. 然而, 慢性昼夜节律紊乱或*Per1*基因的缺失在削弱其细胞因子分泌能力的同时, 还会减弱对感染细胞的杀伤能力^[70,71]. 除此之外, REV-ERBa的缺失可减少肠系膜淋巴结和大肠中NK细胞的频率和数量^[72]. 中性粒细胞大量浸润肠道黏膜并释放ROS, 加重了IBD的炎症与组织损伤. 在人类以及小鼠休息阶段时, 外周中性粒细胞数量下降, 然而到了活跃阶段就会增加^[73,74]. 此外, 中性粒细胞转录和迁移特性的昼夜变化, 是由*Bmal1*借助依赖性自分泌CXCL2机制进行调控的^[75]. 然而, 在肠道当中尚未检测到中性粒细胞类似的昼夜节律振荡. 核心生物钟分子调控免疫细胞相关基因的表达, 影响其发挥吞噬、迁移及炎性因子分泌等作用的节律性, 进而导致肠道微环境等整体生理状态发生昼夜变化, 从而在多层级维持免疫应答的时序性平衡.

2.4.2 昼夜节律调控适应性免疫系统

T淋巴细胞亚群的失衡以及促炎细胞因子的过量分泌是诱发IBD的核心机制. 人体外周T细胞的数量一般在夜间增多, 而在清晨, 由于皮质醇浓度较高的影响, 其数量会出现明显下降^[76,77]. CD4⁺和CD8⁺作为效应T细胞的主要亚群, 其激活后的增殖、分化以及细胞因子分泌, 同样体现出明显的昼夜节律特性^[78]. 尤其是在分泌IFN- γ 以及IL-2的进程中, 研究发现其峰值于夜间21点前后出现, 而低谷于早上6点左右出现^[79]. 此现象与*Clock*和*Bmal1*对T细胞增殖及功能的精确调控相关^[80,81]. 肠道和脾脏中TH17细胞的昼夜节律性分化及功能性表达受到REV-ERBa的调控. REV-ERBa可以直接结合到NFIL3的基因序列上, 抑制其转录表达. 其中转录因子NFIL3能够直接结合和抑制*Roryt*启动子区域; 同时, REV-ERBa通过招募组蛋白去乙酰化酶3(histone deacetylase 3, HDAC3), 使得染色质结构变得“紧密”, 从而强力抑制*Rorc*基因的转录和ROR γ t蛋白的表达, 进而抑制TH17细胞的分化^[82,83]. 白细胞作为适应性免疫系统中另一关键的免疫细胞, B淋巴细胞利用自身抗体生成及细胞因子分泌, 参与到IBD免疫失调里. 在外周血以及淋巴结中, 夜间时B细胞的数量达到顶峰, 而后在白天逐步回落, 这种节律性的波动主要是因为细胞从血液中有规律地回到淋巴结造成的^[84]. 研究发现, 轮

班工作引发的昼夜节律紊乱会降低体内IL-10 B细胞的免疫抑制能力,血液内CLOCK蛋白水平提高,且和IL-10 mRNA水平呈负相关联系^[85]。*Bmal1*的缺乏会引发血液和脾脏中B细胞数量下降,并且CLOCK蛋白表达改变与调节性B细胞释放IL-10的免疫抑制功能有关^[86]。然而,有研究指出,B细胞特异性*Bmal1*缺失的小鼠,其B细胞分化和功能方面没有出现任何改变,这可能是由昼夜节律与组织微环境的共同作用导致的^[86]。总体而言,昼夜节律借助调节免疫细胞的数量和功能,对适应性免疫系统的稳定状态和反应能力起到极为关键的作用。采用靶向昼夜节律以调控适应性免疫,有望为IBD的治疗提供新的策略。

2.4.3 昼夜节律调控信号通路

IBD的发病机制跟多种关键炎症信号通路的异常激活密切相关,NF- κ B信号通路对肠道炎症反应的调控起着极为关键的作用。研究显示,NF- κ B的活化表现出明显的昼夜节律,其激活程度在12点达到峰值。生物钟分子可在多个维度上精准调控NF- κ B信号通路。CLOCK作为NF- κ B的转录共激活因子,在含p65亚基的NF- κ B蛋白质复合物中,能够独立于BMAL1通过乙酰化修饰直接强化NF- κ B的DNA结合能力^[87]。*Bmal1*基因能够驱动长链非编码RNA(Lnc-UC)的节律性表达,进而激活Rev-erba基因,而Rev-erba通过间接抑制NF- κ B信号通路的活性,从而在肠道中建立起一种昼夜节律性的抗炎保护机制^[88]。在生理状态下,BMAL1与CLOCK形成BMAL1-CLOCK-E-box复合物抑制NF- κ B活性;而在炎症状态下,NF- κ B能够破坏并减少复合物的形成^[89],从而释放CLOCK并酸化NF- κ B亚基p65,进一步放大NF- κ B的转录活性,形成恶性循环。这正是IBD病情不断恶化的原因之一。此外,生物钟分子调节因子如Rev-erba与Rora,同样能抑制肠道上皮细胞中NF- κ B信号通路的转录表达,以此减轻DSS引发的UC肠道损害^[68,90]。JAK/STAT信号通路过度激活可促使促炎因子释放,从而加速IBD病情的进展。研究表明,JAK-STAT信号通路的相关表达产物呈现出昼夜节律性变动,STAT基因表达水平于傍晚达到最高点^[91]。微小RNA可直接影响生物钟分子的表达^[92],并且还可借助靶向抑制JAK/STAT配体Upd,调控生物钟分子的输出信号。CRY1和CRY2通过其C端的核输出信号(nuclear export signal, NES)在细胞质中与JAK2结合,抑制其与STAT5B的相互作用,从而影响JAK-STAT的转录^[93]。炎症因子(IL-1 β 、IL-22及IL-12等)作为IBD相关信号通

路中的效应分子兼信号放大器,与生物钟分子(如*Bmal1*、*Per3*及*Nfil3*等)有着紧密的联系^[94-96]。总之,昼夜节律在信号通路转录与翻译过程的调控里起着极其关键的作用,而且在IBD的发病机制里扮演核心角色。

综上所述,肠道微环境的稳态依赖于菌群-屏障-免疫系统之间紧密的相互作用,并且昼夜节律在这个过程中起到了关键的调节作用。IBD患者通常伴随着严重的CRD,这种紊乱状态往往会诱发并加剧肠道菌群失衡、屏障功能的损害程度以及免疫反应的异常激活,最终导致IBD持续恶化,并可能增加结直肠癌的发病风险系数。为此,该调控网络凸显了昼夜节律作为肠道稳态“时间开关”的核心作用,为精准开展IBD干预提供了潜在的作用靶点。

3 IBD的时间医学策略

时间医学(chronomedicine)是一门研究时间与人体生理及病理变化之间关系的学科。在IBD治疗的相关领域,时间医学策略正逐渐受到重视。时间医学治疗关键之处在于优化治疗时机、调整昼夜节律以及靶向节律相关通路,可以有效地增进IBD治疗效果,削减药物引起的副作用。

3.1 调节昼夜节律药物

研究表明多种激素、维生素与小分子之类的药物在调节生物钟分子表达及治疗IBD方面潜力显著。小分子调节剂对核心生物钟分子加以干预,在疾病的治疗里起到重要功效。TAK-828F属于小分子ROR γ t反向激动剂,可有效抑制ROR γ t的活性。在IBD患者的血细胞中,TAK-828F可明显降低促炎细胞因子的分泌量。此外,它通过调节免疫功能系统并对肠道屏障进行修复,由此减轻了UC模型小鼠身上的炎症反应^[97]。REV-ERB α 激动剂SR9009凭借激活小鼠体内Rev-erba的表达,可高效地抑制肠道NLRP3炎性小体,进而有效缓解DSS诱发的结肠炎症状^[68]。褪黑素因其能够调节哺乳动物睡眠-觉醒周期的显著作用而备受人们关注。补充添加褪黑素不仅可缓解时差反应,也能改善UC患者的症状^[98]。此外,服用褪黑素有助于恢复肠道通透性,调整炎症所引发的级联反应,改善肠道菌群结构和活动节律性,并降低UC患者疾病的活动水平^[99-101]。一项评论报告显示,超过半数的IBD患者有微量元素缺乏的问题,诸如铁、叶酸和维生素D等^[102]。目前已证实维生素D可通过调控褪黑素的合成来影响昼夜节律,并运用其

核受体调控多种昼夜节律基因的表达活动^[103,104]。补充维生素D不仅可以实现对DSS诱导的小鼠肠道上皮屏障的修复,推动微生物群回到稳态水平,还能够显著降低IBD患者的C-反应蛋白水平、临床活动评分及复发率^[105,106]。肠道微生物代谢产物指的是肠道微生物群在代谢时产生的各类小分子化合物。源自肠道菌群的代谢物尿石素A,能够恢复UC小鼠肠上皮细胞中*Bmal1*和*Per2*的昼夜节律振荡,同时降低炎症因子的表达水平,且增加了紧密连接蛋白的表达水平^[107]。作为SCFAs的主要成分之一,补充丁酸钠可明显抑制UC患者的炎症水平发展,促进*Bmal1*、*Per1*及*Cry1*的表达水平,进而改善睡眠质量^[108]。因此,具有调节昼夜节律功能的外源性化合物可作为针对IBD的辅助治疗手段,尤其适合有睡眠紊乱症状的IBD患者。

3.2 时间药理学

药代动力学、药效学和药物代谢存在昼夜节律上的变化。目前,研究者愈发留意选择一天中合适的时间去给药,并且着重基因表达与细胞过程里的昼夜节律变动。据报道,80%以上FDA批准的药物,针对的是呈现出昼夜节律的细胞过程^[109]。择时给药是一种依照“时间生物学”原理的前沿治疗策略,其核心是依据人体昼夜节律调整优化给药时间,以求增强药物疗效、减少剂量,并且降低副作用出现。IBD患者往往表现出药物代谢及处置的明显变动。Yang等人^[110]研究发现,UC显著影响了小鼠体内细胞色素酶P450(cytochrome P450, CYP450)的表达,在ZT8时UC小鼠的CYP1A2和CYP2E1蛋白表达较对照组降低约40%~60%,而在ZT20时则恢复至正常水平。这种差异直接导致茶碱代谢速率在ZT8时下降50%以上,血药浓度-时间曲线下面积增加3倍,并诱发显著肝毒性;而在ZT8时代谢参数与对照组无显著差异。通过进一步发现,UC小鼠BMAL1的核转位能力在ZT20时受损,导致其与二者基因的启动子区域的E-box元件结合效率降低,而给予REV-ERB α 拮抗剂可改善此现象。这一发现表明,在IBD患者中的药物治疗中,需检测患者外周血中代谢酶及节律基因的表达水平,同时监测用药48 h后药物血浓度以便计算实际代谢率,从而预测其对药物毒性的昼夜易感性;应避免药物代谢酶昼夜节律低谷期进行治疗,或采用“高峰期增量、低谷期减量”的分时段给药策略。目前试验发现,IBD治疗效果具有显著时间依赖性。例如,IBD的治疗效果明显受时间因素影响,临床上

IBD患者早晨服用6-巯基嘌呤,比起夜间服用,更有利于优化代谢产物水平,进而得到更良好的治疗效果^[111]。在小鼠模型中,陈晔光课题组^[112]通过不同时间点(ZT0或ZT12)灌胃的方式构建DSS诱导的UC小鼠模型,结果显示,在静息期(ZT0)的UC小鼠表现出更严重的症状并且IEC中*Bmal1*的表达达到峰值,而活跃期(ZT12)处于最低水平。随后给予小鼠SR9009可抑制*Bmal1*表达,并发现在ZT0时(*Bmal1*表达最高时)给药,可显著缓解DSS诱导的结肠炎,且疗效优于其他时间点。表明*Bmal1*通过激活凋亡和炎症通路促进结肠炎的发生。此外,Zhou等人^[113]不同时间给予UC小鼠小檗碱进行干预,发现相较于ZT2时给药,小檗碱在ZT10时给药在减少结肠组织病理损伤现象、降低炎症因子的表达水平以及提升紧密连接蛋白表达能力等方面,都展现出更明显的治疗成效。其作用原理是在ZT10时可最大程度地增加*Rev-erba*的表达,进而影响其下游诱导炎症反应、细胞增殖以及细胞分化等相关的基因表达。总之,择时给药取得更佳疗效的关键是因为在药物作用在关键时间窗口内,例如疾病的活动指标、节律基因的表达水平以及药物的吸收和代谢能力均处于某种峰值情形。因此,依据前文所做的IBD患者病理特征、节律基因振荡以及肠道微生态中菌群和细胞节律性变化的分析,提示择时给药及联合用药策略具有精准干预的潜在价值。

3.3 限时禁食

SCN可以结合机体外周生物钟系统对胃肠道运动的昼夜节律起双重作用。胃肠道在非禁食时,胃肠道的节律受中枢SCN的主要调控;若处于正在进食时,食物信号可直接作用于肠道神经元及平滑肌使得肠蠕动增强^[31,114];还可诱导肠道外周生物钟分子(如*Clock*、*Bmal1*)的表达水平在进餐时或饭后的升高^[115],且正如前文所描述:改变小鼠喂食时间后出现OTUs昼夜节律振荡约12 h相移的现象^[48]。这些结果印证了饮食因素独立于SCN调控胃肠运动。因此,限制饮食作为一种干预方法可以调节IBD相关的CRD。研究表明,Moro等人^[116]通过招募健康受试者接受进行为期12个月的限时进食(time-restricted eating, TRE),其在能量消耗后进行8 h进食(13:00、16:00和20:00),从而构成16 h的禁食期。与正常饮食(8:00、13:00和20:00)相比,TRE受试者血清中炎症标志物IL-6、IL-1 β 和TNF- α 分别下降24.4%、10.9%和8.3%。Chen等人^[117]对健康受试者进行30天的TRE管理(9:00~17:00),与正常正常饮食相比,

TRE干预能够降低IL-6、TNF- α 水平及衰老T细胞比例,同时增加抗衰老代谢物(鞘氨醇-1-磷酸、 α -酮戊二酸)及抗炎菌属(阿克曼菌属及理研菌属)的比例。Zeb等人^[118]通过招募健康男性受试者进行为期接受25天的TRE,仅允许在8 h(19:30~3:30)内进行无食物限制的正常饮食,其余16 h禁食。与没有时间限制常规饮食相比,TRE显著增加肠道有益菌群(普雷沃氏菌科和拟杆菌科)的丰度,并且通过激活Sirtuin-1(SIRT1)增强昼夜节律基因(*Bmal1*、*Clock*)的表达。Xie等人^[119]进一步探究不同时间段的限时进食是否具有效果差异,为此,将健康受试者被随机分为早期TRE组(进食时间为:6:00~15:00)、中期TRE组(进食时间为11:00~20:00)。结果显示,早期TRE在胰岛素敏感性、炎症标志物(IL-8、TNF- α)的下降、体脂率和外周血生物钟分子蛋白(BMAL1、PER2和SIRT1)表达水平增加的方面上都要优于中期TRE。Polidarová等人^[120]将大鼠(夜行性活动)通过30天持续光照刺激SCN诱导CRD,期间动物自由摄食。干预组于第15天起,在持续光照下给予ZT3~ZT9期间的进食,其余时间进行禁食。与自由进食相比,TRE能够恢复结肠中*Per1*、*Bmal1*和*Rev-erba*基因的节律性表达。Niu等人^[121]指出,对IL-10缺失小鼠诱发慢性UC模型实施夜间TRE,具体方案为:初始3天实施8 h TRE(ZT13~ZT21),随后3天改为6 h TRE(ZT13~ZT19),最后进行为期4周的4 h TRE(ZT13~ZT17)。与自由进食相比,TRE能够显著减少促炎因子(TNF- α 、IFN- γ)的及CD4⁺ T细胞的浸润,逆转了拟杆菌门、厚壁菌门等菌群的昼夜节律消失,显著恢复了BMAL1、PER2等基因的昼夜振荡模式,并且证实BMAL1是TRE发挥作用的关键分子靶点。Song等人^[122]采用DSS诱导的小鼠UC模型并利用TRE(进食时段为ZT12~ZT18)与模拟禁食饮食(fasting-mimicking diet, FMD, 热量相当于正常饮食的30%)这两种饲养方式开展研究。发现TRE和FMD均可增加了结肠隐窝的数量、减少全身局部炎症并降低了组织学评分。但FMD在治疗UC方面比TRE具有中等更好的效果,其原因在于FMD还可以增加结肠中Lgr5⁺细胞和增殖标志物的数量。然而,错误时间的进食(小鼠光照/休息期间)能够引起外周-中枢昼夜节律不同步,导致结肠*Per2*表达紊乱,并破坏糖吸收蛋白SGLT1的节律性^[123]。总而言之,在进食时应优先选择晨间进食窗口,同时应避免摄入较高热量食物。此方法能够通过光-食物信号协同优化昼夜节律,改善肠道菌群、机体代谢水平和减少炎症反应,为治疗IBD等炎症

性疾病提供了新的思路和潜在干预靶点。

3.4 光照与睡眠

光照和睡眠对昼夜节律的调节起到关键作用,能够直接影响SCN,从而实现对全身生物钟分子表达模式的调控。光照疗法(bright light therapy, BLT)是指机体接受光照的一种非侵入性疗法。研究表明,BLT可推迟并纠正由时差或者轮班工作造成的昼夜节律紊乱^[124,125]。此外,BLT还有助于调节IBD患者紊乱的昼夜节律。Cohen-Mekelburg等人^[126]对68名IBD患者进行每日清晨30 min高强度白光照射(强度约10000勒克斯,460~480 nm波长)以此模拟自然晨光,并持续干预4周。结果显示,这种疗法可对患者的睡眠质量、情绪状态以及胃肠道症状起到改善作用。Guadagnoli等人^[127]的研究表明,睡眠不足是引起IBD患者次日疼痛和疲劳程度加重的重要因素。与此同时,睡眠障碍可使结肠内多种生物钟分子的表达水平降低,进而导致周期振荡出现混乱,进而提高DSS诱导的UC易感性^[16]。因此,保证合适的光照时长与充足的高质量睡眠,对于稳定机体SCN节律、促进肠道损伤恢复意义重大。

4 总结与展望

IBD在全球发病率正逐年上升,已为公共健康带来了重大困扰。近年来,昼夜节律在IBD发病机制和临床治疗方面的研究逐渐增加(图2)。轮班制的工作、睡眠失调或环境等生物钟分子紊乱因素则可显著增加IBD的发病风险。生物钟分子对肠上皮屏障修复、免疫细胞活化和菌群代谢振荡的调控在维持肠道稳态发挥着不可或缺的作用。虽然近年来生物制剂及小分子药物应用显著优化了IBD的临床管理状况,但患者仍然面临着治疗应答率低、复发率高和长期用药安全性等方面的问题。常规治疗方案主要强调“抑制炎症”,但常常忽略了疾病发生发展的节律时间特性。随着对昼夜节律影响IBD发病机制的逐渐理解,时间医学策略在防治IBD中的更广泛的应用得以体现。具备昼夜节律紊乱调节作用的药物、良好的饮食结构、适当的日光照射、良好的作息规律有可能成为一种安全又有效的辅助治疗途径。此外,针对IBD开展择时给药治疗也是个相对新的研究方向,在实验中已经表现出极大的潜力。需要注意的是个体间肠道昼夜节律的差异会导致对药物代谢产生时空异质性。应该更多地需要药理学、生理学和临床医学的积极参与和协作以进一步的理解和应

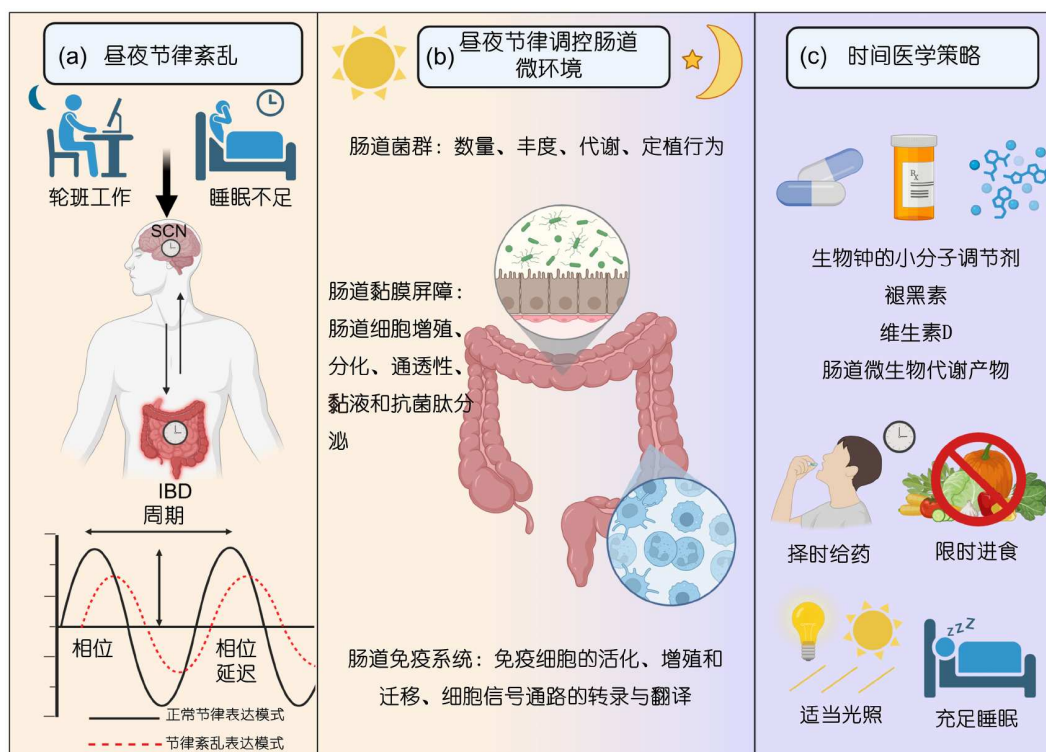


图 2 IBD中的昼夜节律调控机制与治疗策略。(a) 轮班工作或睡眠不足等昼夜节律干扰因素, 可通过异常激活SCN, 导致核心生物钟分子表达相位延迟及振幅衰减, 进而诱发和促进IBD的发生发展。(b) 肠道微环境的稳态, 包括肠道菌群组成、黏膜屏障完整性及免疫系统功能, 均受机体昼夜节律的精密调控。(c) 基于时间医学策略(如择时给药、限时进食、光照调控及睡眠干预), 结合生物钟分子调节剂(褪黑素、维生素D等)的应用, 能够同步化核心生物钟分子表达, 恢复昼夜节律稳态, 进而发挥治疗IBD的作用。图片由BioRender.com制作

Figure 2 Circadian rhythm regulation mechanisms and treatment strategies in IBD. (a) Circadian rhythm disruptors such as shift work or sleep deprivation can abnormally activate the suprachiasmatic nucleus (SCN), leading to delayed phase and attenuated amplitude of core circadian gene expression, thereby inducing and promoting the onset and progression of IBD. (b) The homeostasis of the intestinal microenvironment, including gut microbiota composition, mucosal barrier integrity, and immune system function, is precisely regulated by the body's circadian rhythm. (c) Based on chronomedicine strategies (such as time-restricted feeding, light exposure regulation, and sleep intervention), combined with the application of circadian rhythm molecular modulators (melatonin, vitamin D, etc.), can synchronize core circadian clock gene expression, restore circadian rhythm homeostasis, and thereby exert therapeutic effects on IBD. Created with BioRender.com

用这种治疗策略。

尽管目前许多时间治疗手段在临床上展现出良好的治疗效果, 但基础研究依旧比较薄弱。未来临床上需要做更多的工作是采用个性化医疗方法, 建立IBD患者昼夜节律评估体系, 例如通过可穿戴设备连续监测或开发更精准的节律生物标志物, 从而获得每位IBD患者的昼夜节律表型水平的变化规律, 并把该结果作为患者最佳联合用药方案的基石, 同时为患者提供有关最佳服药、用餐及入睡时间的个性化建议。基于此, 实施

“时间医学+精准医疗”联合干预试验, 探究个体化节律调节方案。在推进这一愿景时仍面临多重挑战: 患者依从性差、医疗机构在夜间进行特定治疗方案也存在条件不充足的情况; 由于每位患者的昼夜节律存在个体差异, 其可行性需充分考虑个体昼夜节律表型评估方法的标准化与可行性(如设备成本、数据分析复杂性)制定个性化治疗方案, 以及该策略在跨时区旅行或轮班工作人群中的适应性挑战。但相信随着对时间医学的不断探究及科学技术的不断发展, 未来有望实现这一目标。

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Summary for “炎症性肠病中的昼夜节律: 从生理基础到时间医学应用”

Circadian rhythms in inflammatory bowel disease: from physiological basis to chronotherapy applications

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Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and recurrent gastrointestinal inflammatory disorder. It is characterized by persistent mucosal inflammation, damage to the intestinal epithelium, and impaired tissue repair. The primary clinical symptoms of IBD include abdominal pain, diarrhea, and bloody stools, with the frequency and severity of episodes often exhibiting a distinct circadian rhythm pattern. Various studies have proven that circadian rhythm disorders (CRD) are implicated in the pathogenesis, exacerbation, and treatment outcomes of IBD. This connection arises from the crucial role that circadian and biological clock molecules play an important role in regulating the diversity and colonization of gut microbiota, modulating mucosal barrier function through the expression of tight junction proteins, and exerting immunoregulatory effects via regulating immune cell activation, proliferation, and migration. However, disruptions to these rhythms often stem from modern lifestyle factors such as shift work, sleep deprivation, or irregular eating patterns. This leads to dysbiosis of the gut microbiota, increased intestinal permeability, and abnormal activation of the immune system, thereby inducing the onset of IBD or exacerbating its progression. IBD symptoms exhibit significant circadian rhythmic fluctuations. For example, disease activity, gut microbiota composition, intestinal mucosal barrier function, and inflammatory cytokine expression levels often exhibit diurnal patterns. Furthermore, drug metabolism and efficacy are also regulated by circadian rhythms, influencing the pharmacokinetic characteristics and pharmacodynamic performance of common IBD treatment regimens, such as glucocorticoids and immunomodulators. For instance, administering certain medications at specific times can enhance bioavailability and reduce toxicity. It suggests the potential feasibility of chronotherapy strategies. Accordingly, this review explores the application prospects of chronotherapy in the management of IBD, including multiple potential pathways that restores circadian synchrony and improve the intestinal microenvironment. These include: timed medication administration that is based on chronopharmacology and disease activity fluctuations, time-restricted eating that means consuming meals within a prescribed window during active phases, and behavioral interventions like adequate light exposure and sleep. These approaches aim not only to enhance therapeutic efficacy, but also to mitigate drug side effects and improve the quality of life for patients, particularly IBD patients with sleep disturbances. In summary, integrating circadian biology into IBD research offers new insights into disease mechanisms and paves the way for personalized time-based therapeutic interventions. Future efforts should further advance clinical translational studies to identify optimal time windows and individualized treatment strategies for different IBD subtypes. This review synthesizes existing evidence to establish a foundational framework for future clinical research, emphasizing the critical importance of considering circadian rhythms in IBD management and treatment.

inflammatory bowel disease, circadian rhythm, gut microbiota, gut immunity, chronomedicine, timing treatment

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