

肠道微生物与皮肤疾病——肠-脑-皮轴研究进展

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摘要 皮肤疾病, 特别是湿疹、皮炎和痤疮等不仅影响个人形象, 还可引起躯体感觉不适或精神异常。皮肤疾病影响人群广泛, 病因复杂, 复发率高, 全球范围内患病人数不断增加。皮肤疾病与心理疾病之间存在密切联系, 并且心理疾病的患病比例增长趋势也很明显。近年来的研究表明, 肠道状态、肠道微生物以及心理疾病与皮肤疾病的关联称作肠道-大脑-皮肤轴(肠-脑-皮轴)。肠道微生物可影响皮肤疾病的发生, 并且精神状态与肠道微生物健康状况可折射皮肤健康状况。反之, 皮肤状况也可作为精神状态和肠道微生物健康状况的评估参照。饮食是通过肠-脑-皮轴影响皮肤的重要因素, 而心理因素对皮肤健康的影响也不能忽视。通过将肠道和皮肤微生物、肠道状态、大脑以及皮肤作为一个系统, 而非独立对待, 进而围绕肠-脑-皮轴进行干预将是解决皮肤疾病的重要方法。未来皮肤病的治疗趋势是将饮食、益生菌、益生元、药物和心理健康等方式综合运用。本文将重点介绍人类第二基因组——人体微生物组、肠道-大脑-皮肤轴与皮肤疾病的关系以及相互影响有关的研究进展。

关键词 皮肤, 肠道, 大脑, 肠-脑-皮轴, 肠道微生物

皮肤是人体暴露面积最多的器官, 也是保护机体内各种组织和器官免受物理、化学、病原微生物等侵袭的前线。在全球范围内, 皮肤疾病的患病率日益增多。据统计, 全球最常见的皮肤病——粉刺(或称痤疮、青春痘, *Acne vulgaris*), 大约会影响80%的青少年到青壮年^[1], 仅在美国就导致每年30亿美元的财政损失^[2]。皮肤免疫疾病——牛皮癣(或称银屑病, *psoriasis*)影响全球2%~3%的人群^[3], 过敏性皮炎(atopic dermatitis, AD)则有10%~20%的儿童患者^[4]。

值得注意的是, 心理问题发生的比例在逐年升高, 伴随而来的皮肤病呈增高趋势。研究人员注意到, 皮肤疾病与精神疾病具有共病性, 诸多基础和临床研究发现精神心理因素在皮肤病发病中起特定作用^[5]。皮肤病人数多、病因复杂、复发率高, 不仅影响患者的面容、降低美感, 常伴有疼痛、剧烈瘙痒或

皮肤干燥等躯体感觉, 甚至引起自卑、消极、焦虑、抑郁等心理疾病, 严重影响患者生活质量, 加重个人和社会经济负担。因此, 防治皮肤疾病已经成为亟待解决的世界性难题。皮肤病的病因复杂, 通常使用针对患处的单纯性治疗方式, 可能收效甚微。近年来研究表明, 肠道微生物与多种皮肤疾病关系密切, 针对肠道微生物的研究正在逐步破解这一难题。本文将重点综述肠-脑-皮轴(gut-brain-skin axis), 并讨论心理疾病、肠道微生物与皮肤疾病之间的关系。

1 皮肤与心理状态的关系: 脑-皮联接 (brain-skin connection)

在几十年的临床观察中, 人们意识到皮肤疾病与心理疾病之间在发病时间和严重程度方面同步或重叠。随着研究的深入, 大脑与皮肤关联逐渐清晰,

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并且已组成专业的神经皮肤病学或精神皮肤病学研究组。大脑皮肤之间的关系称为脑-皮连接^[6]。

研究发现,年轻人最常见的痤疮与抑郁、焦虑和其他心理疾病常相伴发病,而相比其他非精神疾病,如癫痫和糖尿病等慢性疾病,年轻痤疮患者的心理健康障碍情况可能更严重^[7,8]。此外,心理应激会加重多种皮肤疾病,特别是免疫性皮肤病,如过敏性皮炎、牛皮癣、脂溢性湿疹(seborrheic eczema)、结节性痒疹(prurigo nodularis)、扁平癣(lichen planus)、慢性荨麻疹(chronic urticaria)、斑秃(alopecia areata)和瘙痒(pruritus sine material)等^[9]。此外,人们还观察到,在心理应激阶段,皮肤的平衡状态和表皮的完整性以及保护功能会受到破坏,皮肤天然抵抗有害微生物的能力丧失,引起一系列皮肤疾病或症状,可能使过敏性皮炎和牛皮癣等加重或恶化^[10]。社会心理应激也会引起皮肤问题,这可能是通过影响神经、免疫系统进而影响皮肤健康,具体途径包括:中枢途径(如下丘脑-垂体-肾上腺, hypothalamic-pituitary-adrenal, HPA)轴和蓝斑去甲肾上腺素(locus ceruleus-norepinephrine, LC-NE)交感神经-肾上腺髓质系统)和外周途径(如皮内HPA轴和外周感觉神经与自主神经释放的介质)^[11]。

现已发现,多种活性物质,如激素、细胞因子、p物质、活性氧等和心理应激引起的皮肤改变中发挥重要作用^[6]。慢性束缚应激会引起小鼠的皮肤出现异常,包括毛发周期性异常,出现自噬现象,并且脂质过氧化水平升高,活化的超氧化物歧化酶、谷胱甘肽过氧化物酶(氧化酶)减少以及自噬标记物微管相关蛋白,如LC 3-II (light chain 3-II)和Beclin-1增加^[12]。同时,这种由束缚应激引起的行为异常也能改变肠道微生物组成^[13]。其他类型的皮肤疾病,如白癜风、斑秃、慢性荨麻疹、系统性红斑狼疮等也都与精神因素密切相关^[14,15]。

2 皮肤与肠道健康的关系:肠-皮联接(gut-skin connection)

皮肤与肠道是人体两个最大的器官,也是人体的外表面和内表面。中医认为:“皮肤主一身之表,可防御外邪侵入;大肠为传导之官,传化物而不藏”。虽然这两大器官在形态和功能方面相差甚远,临床观察发现,皮肤与大肠之间关系密切,皮肤与肠道有非常类似的变化和表现,皮肤疾病能引起大肠病变;

大肠疾病也能引起多种皮肤病,这就是“皮肠同病”。现代医学和生物学的发展,已经证明皮肤与肠道之间确实存在密切联系^[16]。

皮肤除受心理因素影响外,也与胃肠道有关。最具代表性的是肠病性肢端皮炎(acrodermatitis enteropathica, AE),这是一种由肠道对锌的吸收异常引起的遗传性锌缺乏证,皮肤和肠道都会表现症状,出现肢端皮炎、脱发和腹泻^[17]。1953年之前,治疗AE的唯一方法是母乳喂养,直到1974年才发现锌对此病有治疗作用。AE常见于断奶儿童,从母乳转为牛奶时会发病,而换为母乳就会好转^[18,19]。尽管母乳的锌含量低于牛奶,但母乳本身对锌的易吸收性比锌的含量更重要,并且可能母乳中的微生物也起作用^[20]。

其他皮肤疾病与肠道也存在密切联系。痤疮患者出现胃肠道不适的风险非常高。一项针对13215名12~20岁的汉族青少年的研究表明,痤疮的患病率达51.03%;患与未患皮肤病的青少年相比,患者发生便秘、口臭、胃反流等胃肠道症状显著增多,约有37%的腹胀可能与痤疮等脂溢性疾病有关^[21]。

研究发现,口周皮炎与幽门螺杆菌(*Helicobacter pylori*, Hp)感染引起的胃炎之间存在显著相关性,口周皮炎的患者中, Hp感染率均超过85%^[22,23]。某些药物可引起皮肤及肠道的过敏症状。腹泻常用药物氟哌酸可引起全身皮肤瘙痒,四肢及躯干出现皮疹,并伴有全腹弥漫性压痛、肠鸣、腹泻以及大便出现较多黏液等皮肤和肠道症状^[24]。

肠道及皮肤都属于人体与外界环境接触的内外表面,它们具有类似的信号转导和神经支配通路。T细胞介导的免疫反应通常会引起肠道和皮肤的双重表现^[25]。我们认为,皮肤和肠道表现呈生物学二态性(dimorphism),在构成免疫屏障方面行使类似功能,只是表现形式不同。

2007~2012年,人类微生物组计划(the human microbiome project, HMP)初步研究报道了人体鼻腔、口腔、产道、皮肤和肠道5个主要部位分布有种类达1000~1500种的微生物,重量达1.5~2 kg,总数量是人体自身细胞数量的10~100倍,编码的基因数量可达人体自身的300多倍,被称为人体的“第二基因组”和“被遗忘的器官”^[26~29]。无论皮肤还是肠道,这些微生物与外界环境之间的关联部分通过附着于其表面的微生物。基于营养、温度、湿度等因素,人体消化道成为世界上生物多样性最为丰富的地方之一,

这些微生物包括细菌、病毒、酵母菌、真菌等^[26~29]。人体微生物与健康关系密切,它们不仅帮助人体吸收和消化营养物质,合成维生素等必需生物活性物质,还可以维护人体免疫系统,抵御病原微生物的侵入^[30]。最新研究发现,痤疮患者皮肤表面的痤疮丙酸杆菌(*Propionibacterium acnes*)的维生素B12的生物合成通路显著下调^[31]。维生素B12都是由微生物合成的,并且需要肠道分泌物的辅助才能被人体吸收,而B族维生素缺乏会导致溃疡、口角炎和皮炎等皮肤疾病,同时影响精神状态^[32~34]。人体微生物广泛参与代谢过程,人体血液中大约70%的物质来自于肠道^[35],其中36%的小分子物质是由肠道微生物产生的^[36]。然而,伴随着社会发展,人体共生微生物的多样性在下降^[37],这种下降可能引起了多种“现代病”,皮肤病高发很可能与此相关。

肠道微生物和免疫系统相互作用,共同进化,能够激活宿主先天性和获得性免疫反应^[38]。研究还发现,肠道与皮肤具有一致的免疫因子IgT (immunoglobulin T),能引发类似的免疫反应^[39]。肠道微生物与免疫系统相关的过敏性皮肤疾病关系也很密切。过敏性疾病的发病机制至今尚不清楚,近年很多研究表明,肠道微生物可能在其中扮演着重要角色^[40]。特应性皮炎或过敏性皮炎(湿疹),在过去30年中发病率增加了2~3倍,在3岁内的孩子中发病率高达44%^[41]。研究发现,成年过敏性皮炎患者粪便中肠道微生物状况与病情严重程度具有相关性,患者粪便中双歧杆菌(*Bifidobacterium*)及乳酸杆菌(*Lactobacillus*)的数量明显少于对照组^[42]。研究还发现,益生菌对该病有一定的防治效果,从而推测肠道微生物可能是发生湿疹的重要影响因素^[43,44]。Noverr等人^[45]于2005年提出肠道微生物引发过敏性疾病的假说,认为肠道微生物对宿主免疫系统的发育成熟具有重要作用,特别是在维持黏膜免疫耐受方面作用显著。

牛皮癣与肠道和皮肤微生物密切相关,肠道或皮肤微生物出现紊乱时会增加银屑病的易感性^[46]。此外,银屑病关节炎(psoriatic arthritis)是一种慢性炎症性关节疾病,也表现为牛皮癣或银屑病等慢性皮肤炎症。研究发现肠道微生物在此病的发病中发挥重要作用,据此提出了皮肤-关节-肠道轴(skin-joint-gut axis)的概念,并且发现Th17 (T helper cells 17)在肠道微生物与银屑病关节炎之间发挥决定性作用^[47]。最近的研究也证明了肠道微生物与关节炎密切相

关^[48,49]。这些研究表明,肠道不仅与皮肤,而且与关节关系密切。

3 皮肤、肠道和大脑的关系:肠-脑-皮轴(gut-brain-skin axis)

皮肤与大脑、皮肤与肠道之间关系密切,而肠道与大脑之间也紧密关联。研究发现,肠道和大脑之间通过迷走神经连接,90%以上的五羟色胺在肠道中产生,并受肠道微生物影响^[50,51]。肠道微生物不仅在皮肤炎症方面发挥重要作用,还能直接影响人体的生理健康以及人的心理和行为^[52~57]。

早在1930年,美国宾夕法尼亚大学的皮肤学家Stokes和Pillsbury^[58]就提出了肠-脑-皮肤统一理论(gut-brain-skin unifying theory)。他们通过一系列实验和临床上出现的奇特现象总结归纳出了皮肤受情绪和精神状态影响的理论和实践机制,认为肠道、大脑和皮肤之间存在密切联系。他们发现,抑郁、担忧和焦虑等情绪状态能改变胃肠道功能和微生物组成,最终导致区域性或系统性的炎症,其中包括皮肤炎症;约有40%的痤疮病人存在胃酸分泌过少的症状,可能胃酸的减少会引起结肠细菌进入小肠,并破坏正常的肠道微生物。压力引起的微生物变化可能引起肠道通透性增加,进而引起区域或系统性的皮肤炎症^[59]。

遗憾的是,这一理论提出之后被商业开发者误解和滥用,出现了各种参差不齐的治疗方法,引起了医学界担忧而最终被定性为伪科学并退场,逐渐被人们遗忘。沉寂几十年后,直到最近才再次被注意^[60]。1981年,研究人员再次发现,一些皮肤、肠道和大脑细胞可能有共同的胚胎起源,证明肠-脑-皮之间的密切关系^[61]。近年来的研究已经确证肠-脑-皮肤统一理论,并且已经有越来越多的研究者将肠道、大脑和皮肤之间的关系用肠-脑-皮轴(gut-brain-skin axis)来表示^[62,63]。肠道、大脑和皮肤之间是通过血液系统、免疫系统、内分泌系统和神经系统进行双向链接的^[6,64](图1)。肠道微生物可以通过影响系统性炎症、氧化应激、血糖控制、组织脂质含量,甚至宿主的情绪等影响皮肤疾病^[60]。

暨南大学医学院的张宏和余林中^[65],早在1999年就发现脂溢性皮炎患者正常的肠道微生物显著失调,包括需氧菌总数与厌氧菌总数明显下降,多种常见正常菌群数量和比例发生改变。

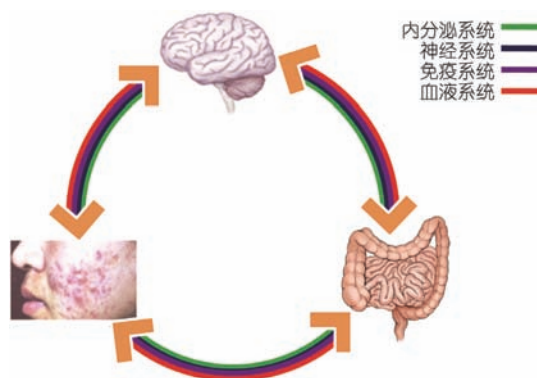


图1 (网络版彩色)肠-脑-皮轴

Figure 1 (Color online) Gut-brain-skin axis

此外,胃酸分泌过少在抑郁病人中非常常见,并且小肠细菌过度生长(small intestinal bacterial overgrowth, SIBO)与焦虑和抑郁密切相关^[66]。酒糟鼻是30~60岁人群中常见的慢性皮肤疾病,该病与肠道微生物关系密切^[67]。酒糟鼻患者出现SIBO的比例比正常人高40%以上,通过治疗改善SIBO后,皮肤病变也能恢复,并且这种治疗效果能够持续至少9个月^[68]。还有研究发现,在消除SIBO后,肠易激综合征病人的心理异常症状得以明显改善^[69]。这些结果表明小肠细菌的异常与精神疾病和皮肤疾病都有关系。

研究发现,痤疮患者中有54%的肠道微生物发生明显改变^[70]。伴有焦虑的肠易激综合征患者血液中大肠杆菌(*Escherichia coli*)产生的脂多糖(lipopolysaccharide, LPS)含量明显增加^[71]。而LPS本身就可以引起动物产生类似抑郁的行为^[72]。

皮肤疾病除受肠道微生物,还受皮肤表面微生物影响。皮肤表面的微生物具有稳定性和部位特异性,同时也受人的生理代谢状态影响^[73]。有研究发现,面部脂溢性皮炎的炎症严重程度与皮肤上的马拉色菌(*Malassezia*)密度呈正相关,而与油脂量无关^[74]。皮肤上的马拉色菌还与脂溢性皮炎、特应性皮炎、马拉色菌毛囊炎、银屑病等皮肤疾病的发生和发展有关^[75]。其他皮肤疾病,如寻常痤疮、牛皮癣、头皮屑(Dandruff)和梅克尔细胞瘤(Merkel Cell Carcinoma)等都与皮肤微生物密切相关^[76]。

肠道微生物对维持正常的皮肤健康具有重要作用。有研究发现,用抗生素给小鼠灌胃消除肠道微生物2周后,小鼠的毛色变得杂乱、无光泽、进食量减少、精神状态变差;用益生菌灌胃10天后,小鼠毛色明显变光泽,精神状态得以改善^[77]。研究还发现,小

鼠摄入乳酸菌(*Lactobacillus*)后,因应激引起的神经性皮肤炎症得以抑制,抑制毛发生长的现象消除^[62]。这说明通过益生菌调节肠道微生物,可以大大降低应激引起的神经性皮肤炎症。调节肠道微生物可影响多种皮肤症状,这是对肠-脑-皮轴理论的有力证明。

随着人们对肠-脑-皮轴的认识,推论肠道微生物对皮肤和大脑的影响机制可能主要通过免疫系统。这是由于肠道微生物是免疫系统最初和最主要的刺激物,对免疫系统的发育和成熟至关重要^[78,79]。

4 肠-脑-皮轴的影响因素

肠-脑-皮轴的影响因素众多,理论上能够影响肠道、大脑和皮肤的任何因素都可影响肠-脑-皮轴,如饮食、光照、年龄、精神压力、药物和环境等。本文仅着重介绍与人体微生物有关的影响因素(图2)。

4.1 食物和营养

食物在塑造和维持肠道微生物方面具有决定作用^[80],而肠道微生物又能进一步帮助人体从食物中获得更多的营养物质。食物和营养能影响肠道微生物组成,不同的饮食习惯肠道微生物组成不同^[81]。动物源食物和植物源食物能够在24 h之内影响肠道微生物,可引起肠道的不同微生物改变,这种改变除受食物本身,还受食物上负载的共生微生物的影响^[82]。

食物不仅影响肠道微生物,也影响皮肤健康状况。饮食可直接影响肠道微生物的组成^[83],同时也是引起痤疮的重要因素^[84,85]。有研究发现,食物中的维生素、类胡萝卜素等微量元素以及不饱和脂肪酸有助于皮肤抗紫外线和防止过敏^[86]。维生素A与皮肤的油脂含量以及表面的pH关系密切,而食物中的总脂肪、不饱和脂肪和单不饱和脂肪与皮肤的水分状况存在密切关系^[87]。食物和营养也影响人的神经系统发育和正常功能,以及人的免疫系统^[88~90]。

19世纪30年代,Stokes和Pillsbury^[58]就曾提出了干预肠-脑-皮轴的方法,他们建议采用添加嗜酸的微生物,如嗜酸乳杆菌(*Bacillus acidophilus*)来终止由压力引起的皮肤炎症。此外,他们还推荐一种嗜酸菌酸奶(*acidophilus milk*)和鱼肝油来辅助治疗皮肤炎症,并且发现口服乳酸杆菌片和乳酸菌发酵饮料有明显促进心理健康的作用^[91]。而饮食和营养对心理疾患具有一定的改善作用已经被多方证实^[92~94]。由

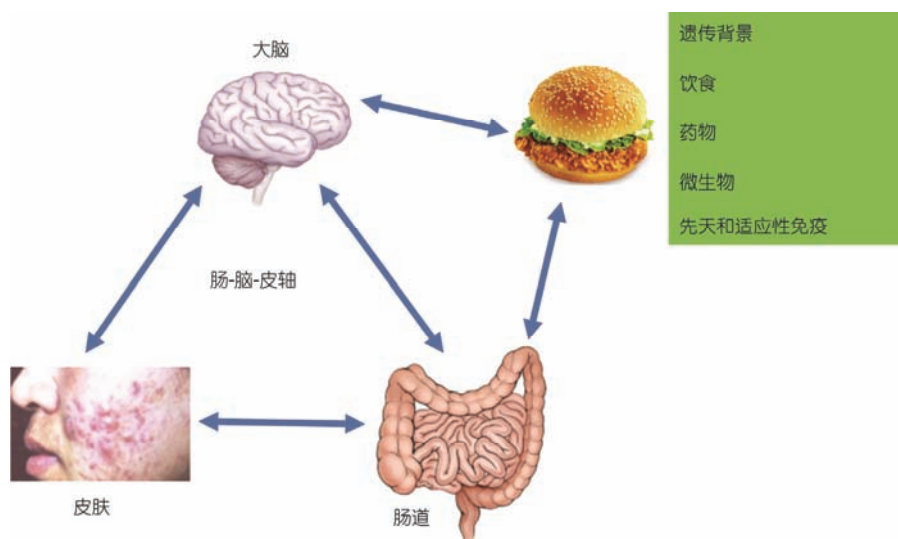


图2 (网络版彩色) 肠-脑-皮轴的影响因素

Figure 2 (Color online) Influence factors of gut-brain-skin axis

此看来, 健康的皮肤离不开合理的食物、营养和益生菌(图3).

4.2 微生物和益生菌

人体皮肤本身的微生物对皮肤的健康至关重要, 它们与肠道微生物一样对维持人体健康必不可少, 其中的常见细菌, 如葡萄球菌(*Staphylococcus*)、棒状杆菌属(*Corynebacterium*)、丙酸菌属(*Propionibac-*

terium)、链球菌(*Streptococcus*)和假单胞菌(*Pseudomonas*)等既具有致病性又能保护皮肤健康^[95]. 因此, 对皮肤微生物的深入了解有助于我们对皮肤疾病的认识. 研究表明, 皮肤微生物受到皮肤解剖结构、位置、宿主的性别、年龄和免疫系统的影响^[73,96]. 皮肤本身的影响因素也很多, 如本身的微生物类型、生存环境、使用的护肤品、化妆品、卫生习惯以及使用的药物等都会对皮肤产生影响^[97~99].

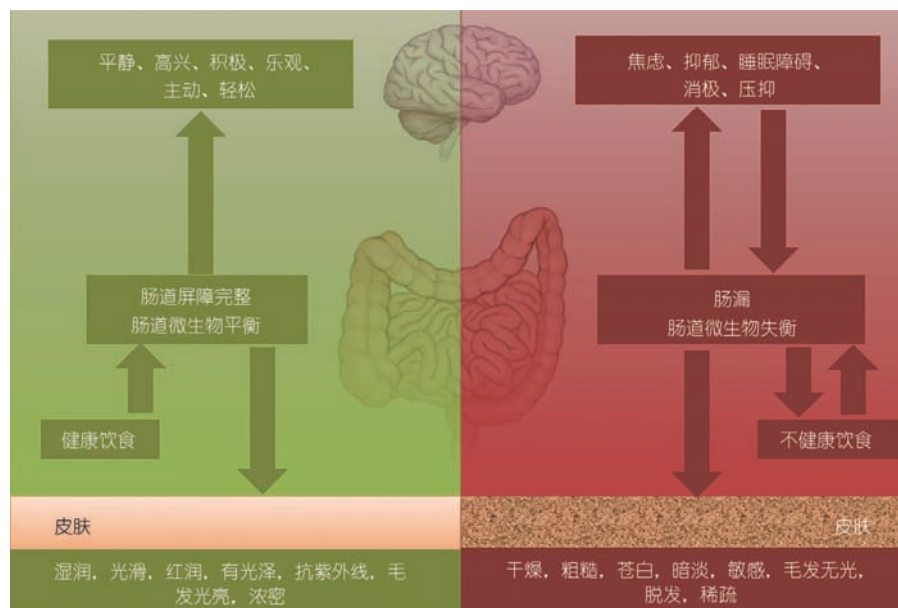


图3 (网络版彩色) 饮食与肠-脑-皮轴

Figure 3 (Color online) Diet and gut-brain-skin axis

“卫生假说(the hygiene hypothesis)”认为人缺少了微生物和寄生虫的刺激,会导致免疫系统异常,引起过敏和哮喘等免疫系统疾病^[100~102]。这一假说同样适用于皮肤疾病。自从人们确定肠道微生物与皮肤疾病之间的生物学关联以来,越来越多的研究开始转向能够调节肠道微生物的益生菌或益生元。

益生菌具有改善肠道屏障功能,恢复肠道微生态健康,刺激宿主免疫系统和对炎症等作用,在预防和治疗皮肤疾病方面有巨大的潜力,不仅用于湿疹、过敏性皮炎、痤疮、过敏炎症或皮肤过敏,紫外线引起的皮肤损伤以及保护伤口,因而也被用作化妆品^[103]。

早在1924年,人们就发现心理异常的病人体内缺乏嗜酸乳杆菌,一些病例研究也发现口服嗜酸乳杆菌之后,痤疮和精神异常症状能够得以恢复^[60]。随后的研究表明,益生菌在改善皮肤状态,缓解或治疗皮肤疾病方面具有潜在价值。长双歧杆菌(*Bifidobacterium longum*)能缓解皮肤炎症^[104]。副干酪乳杆菌(*Lactobacillus paracasei*)能消除P物质引起的皮肤血管扩张、水肿、肥大细胞脱粒和肿瘤坏死因子- α (Tumor Necrosis Factor, TNF- α)的释放,亦可诱导皮肤屏障功能的快速恢复^[105]。来自韩国的研究发现,富含乳铁蛋白(Lactoferrin)的乳酸菌发酵乳饮料能显著降低痤疮患者的皮肤症状,与安慰剂组相比,服用这种发酵乳饮料12周后,脂肪溢出量下降了31.1%,病灶数量和痤疮等级也明显下降^[106]。此外,给年老的小鼠饲喂罗伊氏乳杆菌(*Lactobacillus reuteri*)单菌或发酵乳后,小鼠皮肤变厚,毛色更光亮,生育能力也提高^[107]。随后的研究发现,该菌是通过具有抗炎作用的白细胞介素10 (Interleukin-10)和一种神经肽类激素-催产素来发挥上述作用^[108]。此外,益生菌对皮肤的益处也可能是通过促进肠道免疫系统的成熟,维护正常的免疫系统功能,保持Th1/Th2 (T helper cells 1/2)的免疫平衡、增强调节性T细胞功能及降低血清中Ig E (immunoglobulin E)的水平等调节人体免疫水平来实现的^[109]。最近,我们的一项研究也表明,口服瑞士乳杆菌NS8 (*Lactobacillus helveticus* NS8)菌株能显著改善抑郁大鼠的精神异常症状,并且比药物效果更稳定,同时也注意到动物毛发和皮肤状况的改变^[13]。

4.3 药物

抗生素对肠道微生物有超乎我们预料的重大影

响,长期或过量使用抗生素会增加细菌耐药性,改变肠道微生物构成,甚至破坏肠黏膜,诱发肠炎^[110~112]。研究表明,给变应性疾病动物模型服用抗生素后,肠道微生物明显改变,血清中的Ig E水平显著升高,Th1/Th2免疫失衡^[113]。流行病学调查也发现,婴儿期使用抗生素会增加青少年期患哮喘,过敏性皮炎,过敏性鼻炎等疾病的风险^[114,115]。此外,来自华东师范大学的研究表明,口服万古霉素会使小鼠皮肤伤口处的微生物组成发生明显变化,特别是葡萄球菌减少^[116]。最近的研究还显示,抗生素不仅可以杀死肠道微生物,也能影响大脑细胞可塑性和认知能力^[117]。

5 小结与展望

肠-脑-皮轴对皮肤健康至关重要。微生物、肠道、大脑和皮肤并不是各自独立,而是相互密切关联的复合系统,肠道微生物对维持正常皮肤健康具有重要作用,多种皮肤疾病的发生常伴随精神状态的改变,是通过肠-脑-皮轴产生的影响。

肠道微生物能够通过产生内毒素,刺激免疫系统引起炎症反应或改变营养物质的代谢对肠-脑-皮轴产生影响。其他影响因素,如饮食、益生菌、抗生素和精神因素等同样都能影响肠-脑-皮轴。因此,采取多种影响肠-脑-皮轴方式的干预措施可以明显改善皮肤和心理健康状况。

饮食、益生元或益生菌等调节肠道微生物的方式将成为未来干预和治疗心理和皮肤问题的重要手段。饮食是微生物和皮肤健康的基础影响因素。以头脑欺骗肠脑、暴饮暴食的不良饮食方式,可改变肠道菌群比例或导致肠漏,进而对人体造成系统性伤害。不让“美味”来绑架自己的头脑,理智饮食是防治皮肤疾病的重要举措。

保持好心情有利于大脑向皮肤和肠脑释放更多有益和有积极作用的化学物质,促进皮肤健康,使皮肤真正成为免疫屏障。

目前,益生元或益生菌大多针对肠道微生物而研发和应用,也有一些针对皮肤微生物的研究,它们的使用形式不是口服,而是直接用于化妆品中,涂抹在皮肤上调节皮肤微生物。这种以化妆品形式增补的益生元或益生菌,直接针对皮肤状况,作用更直接^[118,119]。本研究室也在利用含有NS乳酸菌的护肤用品来调节皮肤表面的微生物,获得非常好的效果。

目前正在对使用活性微生物护肤液后皮肤表面微生物的变化以及治疗效果进行进一步分析。

不像肠道内众多厌氧微生物, 我们的皮肤表面布满适宜自然空气成分的微生物, 而多数化妆品并未考虑对皮肤微生物的生活习性, 如金黄色葡萄球菌 (*Staphylococcus aureus*) 和绿脓杆菌 (*Pseudomonas aeruginosa*) 为好氧菌, 涂抹的化妆品一旦阻断这类微生物与空气的接触, 可能导致这类微生物的代谢方式改变而发生感染。皮肤微生物有个体差异性, 化妆品的使用效果与皮肤表面微生物的个体差异密切相关。为了皮肤健康, 不能忽略皮肤微生物的环境和营养。

综合来看, 皮肤不仅是人的第一道免疫防线, 也是精神状态和肠道微生物健康状况的晴雨表。然而,

仍有一些问题亟待解决, 包括: 皮肤微生物和肠道微生物的相互影响; 肠-脑-皮轴的相互影响机制, 特别是免疫系统在肠-脑-皮轴中发挥的作用; 制定合理的皮肤和精神疾病的临床诊疗路径, 皮肤病诊疗可能不仅在皮肤科, 也不能忽略消化科或精神科的正确诊疗; 不同饮食和营养物质对人体微生物, 特别是对皮肤微生物的影响; 借鉴和评估益生菌、益生元、抗生素、甚至粪菌移植等能够改变肠道微生物的方法在干预和治疗皮肤疾病的作用。2016年以来, 国际上全面开展的共生微生物计划将让我们有更多的机会着眼于肠-脑-皮之间的生物学关联, 这不仅为解决不断攀升的皮肤疾病提供了新的视角, 同时也将为认识人类这一复杂的生命体提供更多信息。

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Summary for “肠道微生物与皮肤疾病——肠-脑-皮轴研究进展”

Gut microbes and skin disease, gut-brain-skin axis: A review

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Skin disease, especially eczema, dermatitis and acne, may damage appearance of people, and cause physical discomfort or mental disorders. The prevalence rate is increasing sharply and globally that has been affected all populations in the world. The diseases have various, complex pathogeny and high recurrence rate. Studies demonstrate that skin and mental state are closely related, emerging of skin diseases always accompanied with prevalence of mental disorders obviously.

As early as 1930s, the dermatologist John H. Stokes and Donald M. Pillsbury at the university of Pennsylvania, proposed the gut-brain-skin unified theory. They found a close relationship between the brain and the skin. Recent studies demonstrate a mechanism among gut microbes unbalance, mental disorder and skin diseases, which has been postulated to the gut-brain-skin axis.

Gut, brain and skin can interplay to each other. Psychological stress can aggravate a variety of skin diseases, particularly autoimmune skin disease, such as atopic dermatitis, psoriasis, seborrheic eczema, nodular prurigo, lichen planus, chronic urticaria, alopecia areata and pruritus sine material etc.

Skin diseases are also closely related with health of digestive system. There are high ratio gastrointestinal patients who suffered from acne simultaneously. Gut microbiota is also involved in the gut-skin connection. The number of *Bifidobacterium* and *Lactobacillus* in feces are significantly less in adult patients with atopic dermatitis, than those of controls. The composition of aerobic and anaerobic bacteria in gut of those seborrheic dermatitis patients are severely changed. Similarly, more than half of acne patients go along with significant changes in the gut microbiota.

Studies indicate that both gut microbiota and mental status affect the occurrence of skin diseases. On the contrary, the skin condition can also be as a barometer of mental health and gut microeubiosis. The treatment through the gut-brain-skin axis can be an important intervention to cure skin diseases. Combination of diet, probiotics, prebiotics, drug and mental health status can be positive factors in skin diseases therapy. Diet may affect the composition of gut microbes directly, and light diet can reduce the acne rate. Probiotics, like *Bifidobacterium longum*, *Lactobacillus paracasei*, *Lactobacillus reuteri* were reported to protect the function of intestinal barrier, help to reestablish intestinal microbiota ecological balance, and intensify the anti-inflammation effects. Some bacteria have tremendous potential in prevention and therapy of skin diseases, including eczema, allergic dermatitis, acne, allergic skin, UV induced skin damage and wound.

Antibiotics can eliminate intestinal microbiota. Two weeks antibiotics treatment in mice may lead to reduce food intake, and messy, dull hair et al., in the opposite, 10 days probiotics drinking recover hair status obviously. Besides, probiotics can also restore the stress caused skin neurogenic inflammation in mice.

In the present review, we aim to focus on the following hot topics around symbiosis microbiome, gut-brain-skin axis and skin diseases. To consider the gut microbiota, the brain and the skin as one combined system, instead of single reason may enhance the effects of treatment. More study should focus on the interaction of skin and intestinal microbiota, as well as the interaction mechanism of the gut-brain-skin axis, especially immune system. We urge scientists and medical doctors to pay more attentions on this field.

skin, gut, brain, gut-brain-skin axis, gut microbiota

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