白塞病相关致病因素研究进展
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Progress of environmental and psychological factors in the pathogenesis of Behçet’s disease

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[Abstract]  Behçet’s disease (BD), also called “Silk Route Disease” due to its predominant prevalence through the Silk Road, is a kind of systemic vasculitis. Genetic, immune and environmental factors are thought to contribute to its pathogenesis, although the precise mechanism remains unclear. Geographical environment, smoking, microorganism and psychological factors are involved in the occurrence of BD. In this review, we outline the roles of the above factors in BD.

[Key Words]  Behçet’s disease; risk factors; geographical environment; microorganism; smoking; psychology

Abstract

Behçet’s disease (BD) is an inflammatory disorder characterized by oral and genital ulcerations, uveitis, skin lesions, and other diverse symptoms. It is considered a systemic disease with an unknown etiology. The prevalence of BD varies significantly across different geographical regions, with higher rates in Mediterranean and Eastern countries. The disease is more common in males and has a strong association with certain ethnic groups.

The etiology of BD remains elusive, with a complex interplay of genetic, environmental, and immunological factors. Genetic predisposition plays a crucial role, as evidenced by the increased disease frequency in certain ethnic groups and family clustering. Environmental factors, such as climate and geographic location, also influence the incidence and expression of the disease.

Environmental factors, such as geographical location and climate, have long been considered important in the manifestation and distribution of BD. This review aims to summarize the current understanding of how environmental factors, including geographical, climatic, and cultural aspects, contribute to the pathogenesis of BD.

1. Geographical Environment

BD is more prevalent in regions with a Mediterranean or Eastern climate, particularly in countries along historical trade routes such as the Silk Road. This geographic distribution suggests a relationship between environmental factors and the occurrence of BD.

In these regions, the incidence of BD is significantly higher compared to other parts of the world. The disease is rare in regions with colder climates and lower humidity. The geographical clustering of BD cases further supports the role of environmental factors in its etiology.

2. Psychological Factors

Psychological stress and coping mechanisms have been implicated in the development and exacerbation of BD. Studies have shown that patients with BD experience higher levels of psychological distress, anxiety, and depression compared to the general population. These factors may influence disease expression and treatment response.

The stress response can alter immune function and contribute to the inflammatory processes observed in BD. Coping strategies and mental health interventions may be important in managing BD symptoms and improving quality of life.

3. Smoking

Smoking is a well-established risk factor for BD, with studies indicating a higher prevalence of smoking among BD patients compared to the general population. The mechanism linking smoking to BD is not fully understood, but it is believed to involve oxidative stress and immune activation.

Smoking cessation can improve disease control in BD patients by reducing inflammation and oxidative stress. Public health efforts focusing on smoking prevention and cessation programs may help mitigate the burden of BD in affected populations.

4. Pathogenetic Role of Gut Microbiota

The gut microbiota plays a crucial role in the development of BD, with studies showing alterations in the microbial composition in BD patients compared to healthy controls. The gut microbiota can influence immune responses and interact with the host to affect disease susceptibility.

Modulating the gut microbiota through dietary interventions or probiotics may provide therapeutic benefits for BD patients, with the potential to alter disease course and severity.

5. Future Directions

Further research is needed to elucidate the complex interplay between environmental factors and BD pathogenesis. Genetic predisposition, biomarkers, and personalized treatment strategies can be developed based on a better understanding of environmental influences.

Overall, the role of environmental factors in the pathogenesis of BD highlights the need for multidisciplinary approaches in research and care. Collaborative efforts among clinicians, researchers, and public health officials can contribute to improved outcomes for BD patients worldwide.

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部位发现病毒基因片段或抗体。鼠特殊蛋白质为患者皮肤黏膜破损暴露后使病原体更容易进入。

2 病原微生物

病毒与细菌是最常见致病因子之一。早在1937年，Behcet医生就认为BD是特定的病原体引起的，并且极有可能是病毒。随后研究者们相继在BD外周血及唾液、生殖器溃疡中发现单纯疱疹病毒1型（HSV-1）DNA以及与之互补的RNA。基于既往研究以及HSV感染与BD临床表现的部分相关性，Sohn等通过接种HSV，诱导美国癌症研究所（Institute of Cancer Research，ICR）小鼠产生BD样症状，包括口腔、生殖器及皮肤溃疡。症状持续存在，而将伐昔洛韦给予这些小鼠，以上症状有所缓解。这是目前最成功的动物模型。然而，相当部分研究者并未在外周血或病变部位发现病毒基因片段或抗体。Scoudi等通过较大规模研究报道了BD与健康对照的血清HSV抗体水平无统计学差异，仅检测到1例BD患者唾液中HSV-1载量阳性。这与既往研究结果不一致。上述理由以及此后随机试验中BD对抗病毒治疗的无效性，使得病毒感染不能完全解释BD的发病机制。因此推测HSV参与了BD的免疫机制，但并不亚于单一的病因。亦有研究报道，在外周血发现其他病毒如细小病毒B19、巨细胞病毒、人乳头瘤病毒等抗体滴度阳性。但是，这些感染可能是因患者皮肤黏膜破损暴露后使病原体更容易进入而引发，也可能是免疫抑制剂治疗后产生的机会而感染。需要进一步研究来揭示感染和疾病发生的时间顺序。

热休克蛋白（heat shock proteins，HSPs）是一组进化高度保守的蛋白质，是机体受刺激后产生的特殊蛋白质。有研究表明HSPs与自身免疫病相关，如系统性红斑狼疮、类风湿性关节炎等。人类HSP60与链球菌HSP65存在60%的同源性，分布于革兰氏阳性和阴性细菌中。HSP65与链球菌HSP65之间同源性超过90%。既往研究表明，链球菌可能参与BD的发病。另外，有研究显示，部分BD患者外周血中存在特异性抗HSP27的抗体。Doino等报道BD患者唾液抗HSP60的抗体水平无统计学差异。

3 吸烟

既往研究发现，大气污染颗粒会引发呼吸系统疾病、传染性和癌症等疾病，并推测可能是由于大气气溶胶颗粒中存在的一氧化碳、氮氧化物和重金属等。此外，Lee等报道，肺气肿病复发高峰为春季，与大气气溶胶颗粒中存在的一氧化碳、氮氧化物和重金属等有关。这些因素可能参与了肺气肿病的炎症反应。

吸烟是研究较少的环境因素之一。有研究认为吸烟对BD溃疡有一定保护作用。Aramaki等报道HLA-B51与吸烟，尤其是二者同时存在，是慢性进行性神经白塞病的危险因素。其原因可能与骨髓转移酶(glutathione S-transferases，GSTs)缺乏有关。GSTs是体内生物转化最重要的代谢酶之一，是细胞抗氧化的重要解毒系统，与人体对香烟烟雾中化学物质的解毒有关。GSTM1、GSTT1具有基因多态性，其无效基因型（GSTM1 null和GSTT1 null）可引起相应酶的表达缺失或活性降低，导致解毒功能改变。Ozer等发现GSTM1和GSTT1无效基因型在BD和对照组分布频率存在差异。携带GSTM1无效基因
型的非吸烟女性患者发生结节性红斑的风险降低。GSTM1 无效基因型似乎与大血管血管炎有关，尤其是男性吸烟患者。携带 GSTT1 无效基因型的吸烟男性患者发生静脉功能不全的风险增加。香烟中的某些物质可能会加重 BD 症状，而某些化学物质和氧化应激可能会缓解 BD 症状。Soy 等[23]对长期吸烟的和从未吸烟的无症状 BD 患者进行随访研究结果显示，吸烟组戒烟 1 周后溃疡发生率明显高于不吸烟组；戒烟可加重皮肤黏膜症状，尤其是口腔生殖器溃疡患者。香烟中的尼古丁，可作用于烟碱乙酰胆碱受体，减少 IL-8、IL-10 等炎症因子的产生。这可能是戒烟后溃疡加重的原因之一。但烟雾中有超过 4000 种物质，并不能确定哪一种对 BD 产生作用。

4 肠道菌群

随着分子生物技术的发展，肠道菌群与疾病的相关性成为研究热点。肠道菌群与机体之间存在动态平衡，肠道微环境改变后，肠道中的条件致病菌或其产物激活肠道免疫系统，导致肠道上皮细胞功能障碍及免疫调节受损。肠道菌群失调与自身免疫性疾病、心血管疾病、糖尿病、癌症、肠相关性疾病的患者均有关联。Consolandi 等[26]首次报道了与健康同居者相比，BD 患者肠道菌群失调且丁酸盐减少。其中罗氏菌属和八叠球菌属减少，而此二者为肠道内产生丁酸盐的主要细菌。短链脂肪酸，尤其是丁酸酸对维护肠道功能具有重要作用。其可由多种机制诱导 Treg 细胞分化，从而影响免疫调节。Shimizu 等[27]亦报道了 BD 存在肠道菌群失调，表现为双歧杆菌和乳杆菌增加，而梭菌减少。双歧杆菌和乳杆菌是产生乳酸盐的主要细菌，无菌小鼠口服双歧杆菌后可快速诱导关节炎。而梭菌能够利用乳酸盐分解产生短链脂肪酸。Jo 等[28]研究得出，在有消化道症状而内镜或影像学检查无活动病变的 BD 患者中，三分之一以上小肠细菌过度生长，给予利福昔明治疗 4 周后，85.7%患者症状缓解。

肠道菌群的差异除了基因测序技术的影响，还需考虑种族、地理以及饮食的影响。这可能是上文所述的不同地区 BD 临床表现存在差异的原因之一。但并无确切证据证明肠道菌群失调与 BD 之间存在因果关系，或者在 BD 中存在特定的肠道菌群紊乱。

5 心理精神因素

心理精神因素的多种多样，包括抑郁、焦虑、性格及个性特征等。有报道[29-30]认为 BD 患者的抑郁、焦虑发病率明显高于正常人群。抑郁可兴奋交感神经，使儿茶酚胺分泌增加，影响炎症因子释放，诱使炎症发生；亦可活化血小板，激活凝血系统，使机体处于高凝状态。抑郁患者炎症因子升高，如 IL-6、CRP 等。Karlidag 等[31]研究了应激因素和应答机制在 BD 发病和复发中的作用，发现 70%的患者和 79.4%的患者分别在疾病发生前和复发前存在应激因素。其中 41.2%与社会支持因素有关，如家庭矛盾；17.7%与社会环境有关，如经济困难等。BD 患者比非 BD 患者有更明显的与 BD 相关的生理障碍、抑郁焦虑，并且表现为应对策略缺乏。但目前关于 BD 与心理因素的研究均回顾性研究，存在反向因果关系或者回忆偏倚的干扰，故无法明确是抑郁焦虑诱发了 BD，还是 BD 发生后导致了抑郁焦虑情绪。心理干预能否改善 BD 的情感问题，仍需进一步前瞻性研究证实。

综上所述，BD 具有独特的地理分布、多样的临床表现，其病因及发病机制尚未明确。目前在 BD 发病机制研究方面，一些零散、细小的影响因素常常被忽视。今后应设计合理的试验模型，将部分可能致病的环境因素纳入疾病资料库，有望揭示 BD 的病因和发病机制。

参考文献


[本文编辑] 翟敏，贾泽军