炎症性肠病研究进展

Advances on Inflammatory Bowel Disease

主编　欧阳钦
副主编　张 正　万学红

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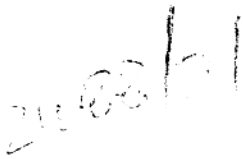

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序

炎症性肠病（IBD）在西方国家已是常见病和多发病，近30年来，溃疡性结场炎（UC）的发病率维持不变，而Crohn病（CD）的发病率则逐渐上升。消化科医师对IBD的熟悉程度并不亚于上消化道疾病。近年，国外对IBD病因及发病机制的研究也十分活跃，动物模型、体外实验研究、临床观察和循证医学证据表明，环境、遗传及免疫紊乱因素均可能参与IBD的发病。因此，已出现了不少针对免疫调节机制的新型免疫疗法，如使用TNF-α单抗治疗CD等，取得了满意疗效。我国过去一直认为IBD较少见，而对其不够重视，最近20年来这一现象虽有所改变，但因研究起点低、深度不够，且治疗试验文章较少随机对照，因而需在临床科研方法学上加以提高。

华西医科大学附属第一医院以欧阳钦教授为首的消化内科多年从事IBD研究，尤其对IBD的病因及发病机制等进行了基础与临床相结合的研究。近年来，该院在欧阳钦教授的领导下，其研究小组在动物模型及细胞免疫研究方面取得了令人瞩目的成绩，研究方向明确，且有一定深度，是我国IBD研究的楷模。

这次华西医科大学附属第一医院受中华医学会消化病学分会委托，承办全国炎症性肠病学术会议。组委会特邀5位国外知名学者和13位国内专家进行讲学，并将专家发言稿与全国各地来稿汇编成册，以期国内消化科医师能对当前国内外IBD研究的最新动态有一全面认识和了解。跨世纪中国的IBD发病率会逐步增高，并将掀起研究IBD的热潮。本次会议将作为一个里程碑，标志着国内IBD研究的新起点与新高潮。

萧树东

2000年9月

前言

诚如多年来我们一直呼吁的那样，炎症性肠病的研究在我国尚处于初始阶段。近年来各地报告病例迭有增加，引起同行的注意。预计随着生活水平的提高、生活方式的改变以及严重的肠道感染的控制，这类疾病的患病率将不断增加。有学者预言，新世纪到来之时也是我国炎症性肠病研究高潮兴起之日。事实上，从近年来的动向，我们已经看到了这一发展的趋势。不少国内同行在此领域的研究，无论是基础还是临床都已取得一定成绩，可谓硕果累累，前景喜人。

在此大好时机，我们接受中华医学会消化病学分会委托，承办全国炎症性肠病学术会议。经过近一年的筹备，邀请国内外专家撰稿，组织大会征文，约请部分研究工作者完成译文和综述。经过大家共同的努力，此次会议资料内容丰富而新颖，至少部分反映了当前国内外研究的进展，对今后基础研究和临床实践均有一定借鉴意义，故决定汇编成册，正式出版，以备同道参阅。

全书包括五章，依次为国外专家讲演提纲、国内专家专题讲座、大会论文摘要、综述与译文、国内外 IBD 诊断标准和治疗指南摘录，以及华西医科大学的 IBD 诊断标准和处理指南等，希望能成为同道的一本专题参考书，对科研起到开阔思路、承前启后的作用，对临床诊治起到规范和指南的作用，使我国炎症性肠病的研究在此基础上大步快走，赶超世界研究水平。

本书在编写过程中，得到了中华医学会消化病学分会专家们的大力支持，得到四川科技出版社的热情帮助，特此致以深深的谢意。

由于编纂时间仓促，加之水平有限，谬误之处在所难免，望同道们在阅读中批评指正，提出宝贵意见。

华西医大附一院

欧阳钦

目录

第一章　国外专家讲演提纲

第二章　国内专家专题讲座

第三章 大会论文摘要

第四章　综述与译文

第五章 炎症性肠病诊断标准和治疗指南摘录

第六章 华西医科大学附一院 IBD 诊断标准和处理指南

第一章 国外专家讲演提纲

1. Causes and Mechanisms of Inflammatory Bowel Disease

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Introduction

Intestinal inflammation is the most common reaction of the digestive system to infectious, immune, toxic, ischemic and other insults. Although the most frequent form of inflammation remains by far an acute self-limited response to infectious bacterial or viral agents, over the last half century there has been a significant and progressive increase of other types of inflammation. They are collectively named inflammatory bowel diseases (IBD), their cause is unknown, they are characteristically chronic and debilitating, and can lead to severe tissue destruction with an increased risk of bowel cancer. The two most common forms of IBD are ulcerative colitis and Crohn's disease, but additional types such as indeterminate, collagenous and lymphocytic colitis also exist. This review will provide a succinct overview of state-of-the-art knowledge on the etiology and pathogenesis of ulcerative colitis and Crohn's disease, and discuss its implication for the treatment of IBD. Whenever possible, some considerations will be included that might be specifically relevant to IBD in China.

Environmental and Genetic Factors

The frequency of both forms of IBD has steadily increased over the last fifty years due to

a real increase of their incidence rather than an improvement in diagnostic modalities[1]. Interestingly, both forms of IBD first appeared in countries of high socioeconomic status, like Northern Europe and North America and subsequently in other parts of the world, including Southern and Western Europe, and more recently South America and Japan. This peculiar geographic distribution over time is believed to reflect subtle but important changes in environmental factors like diet, smoking and exposure to other still undefined elements. In Japan the increase of ulcerative colitis incidence after the Second World War was paralleled by an increased consumption of meat and dairy products[2], but this alone is insufficient to conclude that a modification from a traditionally fish-based diet is responsible for IBD. Smoking is clearly linked to a worse outcome for Crohn's disease but, curiously, has a protective effect in ulcerative colitis[3]. An increased in intestinal permeability has also been proposed as another factor predisposing to Crohn's disease, but if this is a true primary event or one secondary to subclinical inflammation remains to be determined[4]. It is difficult to explain the role of each factor, alone or in combination with others, but a unifying hypothesis is the increased cleanliness of the environment and less frequent exposure to pathogenic agents. This would cause the intestinal immune system not to be challenged early in childhood and become less capable to mount an effective immune response against pathogens later in life[5].

Another important observation is that both Crohn's disease and ulcerative colitis are more common among first-degree relatives that expected by chance alone[6]. This could be due to exposure of all family members to the same environmental factors that predispose to IBD, but an alternative explanation is that the affected individuals share a common genetic background rendering them more susceptible to Crohn's disease or ulcerative colitis. This notion has stimulated an enormous interest in the investigation of genes linked to IBD and a large number of genetic associations and linkages have been reported[7]. At the moment is seems unlikely that a single gene or a limited set of genes will explain all IBD cases. It is more probable that multiple genes favor the appearance of IBD in different populations exposed to diverse environmental agents in each part of the world.

The trend of a progressive increase in the incidence of IBD is continuing, and countries like China are likely to see more a more cases of ulcerative colitis first and Crohn's disease later on, as it has previously observed in other countries. It would be of extreme importance to plan prospective epidemiological studies to track the evolution of IBD in China and potentially define the risk factors in the Chinese population.

Microbial Factors

Since their recognition both ulcerative colitis and Crohn's disease were believed to have an infectious etiology because of their similarities to bacterial colitides like salmonellosis, shigellosis or amebic colitis. The IBD literature is full of studies that have searched for common or unusual bacteria, viruses and fungi, but no microbial agent has withstood the test of

time. During the last two decades attention has been focused on Mycobacterium paratuberculosis, an agent responsible for intestinal inflammation in cattle, and the measles virus as possible causes of Crohn's disease. However, direct recovery of either organism from affected tissues and indirect evidence of their presence by microbiological, immunological or molecular biological techniques have yielded negative or unconvincing results[8, 9].

More recently a different view on the contribution of microbial agents to IBD is gaining increasing acceptance, e. g., that IBD, particularly Crohn's disease, is caused by an abnormal immune response against the normal autologous enteric flora[10]. Two lines of evidence support this view. The first comes from experimental models of IBD, where the majority of animals fail to develop colitis when placed in a germ-free environment. The second comes form a series of studies showing that cell-mediated and humoral immunity against bacterial antigens are enhanced in IBD patients[11], bacterial stasis favor the development of IBD and fecal stream diversion prevents recurrence of Crohn's disease[12], and the beneficial effect of antibiotics and probiotics in some IBD patients[13]. Taken together, these studies suggest that IBD may result from a loss of immune tolerance for the commensal flora. However, until the cause of IBD is found, the possibility that either ulcerative colitis or Crohn's disease are caused by infectious agents cannot be excluded.

The Inflammatory Tissue Response

Even though knowledge of the factors predisposing to or causing ulcerative colitis and Crohn's disease is still incomplete, we have a good understanding of the cells, molecules and mechanisms responsible for chronic inflammation. The mucosal immune system is at the center of all aggressive and protective phenomena occurring in IBD from the very first clinical manifestations to the chronic stage of the disease, and its evolution into complications or remissions[14]. This is a complex and lengthy subject will be discussed in a simplified fashion. All branches of immunity are involved in IBD, with both quantitative and qualitative abnormalities. There is an excess of antibody production in IBD-involved intestine, but there is limited evidence that true antigen-specific autoantibodies play a significant role in tissue injury[15]. Other types of autoantibodies, such the pANCA, have some diagnostic value but they are not involved in mediating inflammation. A variety of functional abnormalities have been reported in regard to mucosal T-cell function which can be summarized as follows: in ulcerative colitis T-cells tend to be hyporeactive, while in Crohn's disease T-cells generally exhibit an enhanced effector function. There are enough data to suggest that Crohn's disease is a Th1-like response, whereas ulcerative colitis has some features of a Th2 response. In addition to classical immune cells, it is also clear that all other mucosal cells (epithelial, endothelial, mesenchymal and nerve cells) actively participate in inflammation, making IBD the outcome of a complex interplay of immune and non-immune interactions[16].

Among the various components of gut inflammation most of the attention has been given

to substances locally secreted that modulate immune responses in the mucosal microenvironment. These include immunoregulatory cytokines such as interleukin (IL) -2, IL-4 and interferon-gamma, immunosuppressive cytokines like IL-10 and transforming growth factor-beta, proinflammatory cytokines like IL-1 beta, tumor necrosis factor (TNF) -alpha and IL-6, and chemokines that attract leukocytes into sites of inflammation, such as IL-8, macrophage chemotactic protein-1, and many others. Interest in these products is justified by the fact that their neutralization can effectively block inflammation and induce remission. In addition to cytokines and chemokines, various other molecules are also important, including growth factors and eicosanoids that can promote healing and cytoprotection, reactive oxygen metabolites and nitric oxide that can be toxic for gut tissue, and cell adhesion molecules that allow communication between different cell types and thus amplify inflammation. The investigation and understanding of how these different classes of molecules work in IBD has been instrumental for the development of rational and innovative therapies as discussed below.

Lessons From Animal Models

During the last decades some of the most significant advances in the cause and mechanisms of IBD have derived from the study of animal models of IBD which allow experiments not feasible in humans and investigate the progress of inflammation over time. Several models have been developed, each with different characteristics, but their discussion is beyond the scope of this review. It is sufficient to state that none of them exactly reproduce all aspects of ulcerative colitis or Crohn's disease[17], but these models have provided crucial new insights with direct implications for human disease. Such implications are summarized in the three following paragraphs:

1) Completely different and independent infectious, genetic or immune defects can cause gut inflammation, suggesting that different causes may trigger human IBD even though the overall clinical manifestations may be the same.

2) Most animal models fail to develop intestinal inflammation in a germ-free environment, indicating that the normal enteric flora is necessary to develop IBD. The same may be true in humans, but whether the whole flora or only selected components are involved is currently under investigation.

3) The animal's genetic background strongly influences the susceptibility and severity of IBD, indicating that although different genes may predispose humans to develop IBD, the type, location, clinical activity and final outcome may be dictated by the unique genetic make-up of each patient.

Finally, beside providing the above critical information, animal models have been instrumental in testing the efficacy of new drugs for IBD.

Concluding Remarks and Therapeutic Implications

The ultimate reason to understand the cause and mechanisms of a disease is to be able to prevent the appearance of disease, eliminate the symptoms, establish a cure, and avoid recurrence. Unfortunately, we are far from this ideal situation, yet recent progress in the etiology and pathogenesis of IBD has been remarkable. This progress has resulted in a totally new approach to therapy resulting from our improved understanding of key mediators of inflammation. Based on this understanding trials are being performed injecting antibodies against anti-inflammatory cytokines like TNF-alpha[18] and adhesion molecules involved in migration of leukocytes into the bowel[19], or administering cytokines with a natural anti-inflammatory activity like IL-10[20]. In addition to biologicals, the use of antibiotics and probiotics will probably become routine in the treatment of IBD[21]. Classical and still effective drugs, such as aminosalicylates and corticosteroids, will not be abandoned but rather combined with the new biologicals and enteric flora modulators, resulting in a more comprehensive and improved therapeutic outlook. Hopefully, all these new treatments will soon become available in China to provide the best possible treatment to local sufferers of ulcerative colitis and Crohn's disease.

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炎症性肠病的病因和发病机制

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肠道炎症是消化系统对感染、免疫、缺血和其他攻击因素最常见的反应。迄今为止，最常见的炎症仍是针对细菌或病毒感染的急性自限性反应。但是近半个世纪以来其他炎症已明显逐渐增多。他们被统称为炎症性肠病（IBD）。其病因尚不清楚，具有慢性和消耗性的特征，可导致结肠癌危险性增加的严重组织破坏。最常见的两种 IBD 是溃疡性结肠炎（UC）和 Crohn 病（CD），但也存在其他类型的 IBD，如未定型结肠炎、胶原性和淋巴性结肠炎。本文将简略回顾有关 UC 和 CD 的病因和发病机制的最新知识，并讨论其对 IBD 治疗的意义。一旦可能，我们应进行一些特别与中国的 IBD 相关