TNBS-COLITIS. CHARACTERISTICS, TREATMENT UND MECHANISM

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Abstract. *Disease states, such as the occurrence of gastrointestinal inflammation (Crohn's disease and ulcerative colitis), can be secondary to a host of determinants that act in conjunction to bring about pathologic change. The underlying factors that mediate the development of such mucosal inflammation has recently been brought to the forefront with the advent of animal models. The examination of these animal models have given researchers a better understanding of the mechanisms involved in the pathogenesis of inflammatory bowel disease. This review discusses one such model, TNBS-colitis, and the insights that it provides into the occurrence of IBD and its future treatment.*

Keywords: *Inflammatory bowel disease; Experimental colitis; Interleukin-1.*

TNBS-КОЛИТ. ХАРАКТЕРИСТИКИ, ЛЕЧЕНИЕ И МЕХАНИЗМ

Аннотация. *Болезненные состояния, такие как возникновение желудочно-кишечного воспаления (болезнь Крона и язвенный колит), могут быть вторичными по отношению к множеству детерминант, которые действуют совместно, вызывая патологические изменения. Основные факторы, которые опосредуют развитие такого воспаления слизистой оболочки, недавно были выдвинуты на первый план с появлением животных моделей. Изучение этих животных моделей дало исследователям лучшее понимание механизмов, вовлеченных в патогенез воспалительного заболевания кишечника. В этом обзоре обсуждается одна из таких моделей, TNBS-колит, и понимание, которое она дает относительно возникновения ВЗК и его будущего лечения.*

Ключевые слова: *Воспалительное заболевание кишечника; Экспериментальный колит; Интерлейкин-1.*

INTRODUCTION

In recent years, a number of murine models of chronic colitis have been developed which are remarkably similar to one or another form of human inflammatory bowel disease. As such, these models provide an excellent opportunity to study the immunopathogenesis and possible treatment of these idiopathic diseases. One such model is TNBS-colitis, a chronic colitis in mice induced by the intra-rectal administration of trinitrobenzene sulfonic acid (TNBS). In the following section we shall discuss our recent studies of this model and show how these studies have led to new insights into the immunologic mechanism underlying Crohn's disease.

CHARACTERISTICS OF TNBS -COLITIS

Characteristics of TNBS colitis TNBS is a classical skin contactant (a chemical compound that induces delayed hypersensitivity reactions when applied to the skin), because it haptenates proteins with TNP groups and renders such self-proteins immunogenic. It is induced in SJL/J mice and a few other mouse strains, by the intrarectal instillation of an ethanolic solution of TNBS, and is characterized by severe colonic inflammation, which increases over 2 weeks and culminates either in the death of the animal or in partial recovery with long-term low-grade inflammation.

Clinical characteristics of this induced disease include diarrhea, wasting, rectal prolapse, a scruffy coat, and a hunched over habitus. As shown, this is accompanied on the histopathological level by a dense transmural mononuclear cell infiltration, loss of normal crypt architecture, and occasional granuloma formation; in short, a pattern not dissimilar to that of Crohn's disease. One important difference between skin contact hypersensitivity and TNBS-induced colitis is that in the skin the reaction is self-limited, whereas in the colon the reaction is persistent. This is likely due to the fact that the effector immune cells called forth by TNBS cross-react with ubiquitous mucosal antigens and thus continue to be stimulated even after the TNP-haptenated proteins have disappeared. There are several pieces of evidence in support of this view. First, as previously mentioned, if lamina propria T cells in a mouse with TNBS colitis are transferred to a naïve mouse, they cause definite colitis in the recipients. Since antigen is not transferred with such T cells, this reaction is probably due to a cross-reactivity with anti gens encountered in the mucosal environment of the new host. Second, IL-2 deficient mice, which have been shown to develop spontaneous colitis under certain circumstances, can be induced to develop colitis within days by the systemic injection of trinitrophenyl keyhole limpet hemocyanin (TNP KLH). This suggests that T cells stimulated by TNP can traffic to the gut, where they encounter cross-reactive antigens and induce colitis. Third, it has recently been shown that T cells from mice with TNBS colitis proliferate in response to exposure from their own flora whereas normal mice do not. This finding implies that in the normal situation a mouse is "tolerant" to its own flora while such tolerance is broken in TNBS colitis.

TREATMENT OF TNBS-COLITIS

One of the predictions of this proposed sequence of events underlying TNBS-colitis is that the latter should be treatable by the systemic administration of antibodies (or other agents) that interfere with the sequence at any one of several stages: in particular, it should be treatable by the systemic administration of anti-IL-12. To formally test this possibility we administered anti-IL-12 to mice either at the same time as TNBS was administered per rectum or after two to three weeks following such administration.

As shown in, these treatment regimens were remarkably effective in that they either completely prevented the development of TNBS-colitis (when given at the time of induction of the disease) or led to dramatic resolution of the TNBS- colitis (when given when the lesion was fully developed). These studies, in showing that a murine model resembling Crohn's disease is treatablewith anti-IL-12, imply that Crohn's disease itself is also treatable in this fashion.

On the basis of this possibility, we are currently planning to test "humanized" anti-IL-12 in clinical trials of patients with crohn's disease (see further discussion below). While the blocking of IL-12 activity with anti-IL-12 may be an efficient way of interrupting the Thl T cell activation pathway necessary for TNBScolitis, it is certainly not the only way the latter can be accomplished.

As indicated above, the critical APC-T cell inter- actions leading to Thl T cell differentiation requires T cell expression of CD4OL on activated T cells and signaling of APC via CD40 for production of IL-12. Thus, it is theoretically possible to interfere with Thl T cell differentiation by blocking the CD40LXD40 interaction. To test this possibility, we administered anti-CD40L antibody to mice at the time of TNBS-colitis induction with intra-rectal TNBS administration. Such treatment did indeed prevent colitis induction as well as the increased IFN--y production in the lamina propria associated with colitis and thus is a second avenue available for the prevention of TNBS-colitis. Whether anti-CD40L can also be used to treat ongoing TNBS-colitis as can anti-IL-12 awaits further study. Another way the Thl pathway can be experimentally thwarted in the context of the TNBScolitis model would be to inhibit more distal inflammatory cytokine effects, either by the administration of anti- IFN-y or anti-TNF-a. In studies relevant to this possibility we found that anti-IFN-7 also inhibited the development of colitis, although such inhibition was not as effective as that achieved with anti-IL-12. Thus, while prevention of TNBS-colitis was inhibitable with a single injection of anti-IL-12, prevention of colitis with anti-IFN-7 required multiple injections and was, in general, not as complete. In addition, wherein mice cured of colitis with anti-IL-12 were not subject to re-induction of colitis with sub-colitis-inducing doses of TNBS, mice cured of colitis with anti-IFN-y were subject to such colitis-induction. This suggests that anti-12-14-treated mice no longer have cells reactive with colitis whereas anti-IFN treated mice have such cells. Important confirmation of this possibility has recently come from the observation that mice with TNBS-colitis treated with anti-IL-12 dis- play large numbers of apoptotic cells in the inflamed colons whereas the same mice treated with display only modest numbers of apoptotic cells at this site.

Overall, then, these studies strongly suggest.

THE MECHANISM OF TNBS-COLITIS

So far in our discussion we have discussed the "how" of TNBS-colitis but not the "why".

In our approach to this question, we were aware of the fact that mucosal responses are normally under the strict control counter-regulatory responses known collectively as ”oral tolerance”. By such responses, encounters between the mucosal immune system and mucosal antigens normally result in tolerance rather than immunity and thus the mucosal immune system is spared of responses that could lead to autoimmunity and/or inflammation. Thus, it seemed possible that TNBS colitis arises because the administration of TNBS per rectum bypasses or subverts the oral tolerance mechanism. In our studies of the role of oral tolerance (or lack thereof) in TNBS-colitis, we took note of the fact that oral tolerance is now known to be due to two independent but interacting processes, the induction of suppressor T cells producing TGF-P (and perhaps other suppressive cytokines) and the induction of clonal deletion and/or anergy. In first of these, the induction of suppressor T cells, is the dominant mechanism of tolerance at low antigen doses and appears to be dependent on the processing and presentation of antigen to T cells in the Peyer’s patches. In contrast, the second of these processes, the induction of clonal deletion or anergy, is the dominant mechanism of tolerance at higher antigen doses and is dependent on the occurrence of “processed” antigen which induces deletion and or anergy not only in mucosal tissues but also in other tissues as well. Emerging evidence shows that this deletional tolerance is independent of suppressor T cell development and the presence of suppressor cytokines. Finally, we also noted that with respect to oral tolerance mediated by suppressor T cells, Th2 T cell cytokines (IL-4) appear to favor suppressor T cell development whereas Thl T cell responses (IFN-y) appears to inhibit the latter.

CONCLUSION

Taken together, these studies suggest that a ying/yang relation between Th1 responses on the one hand and TGF-/3 T cell responses on the other governs whether or not inflammation develops in the gastrointestinal tract. Thus, in normal individuals, the mucosal response set point is shifted towards tolerance and non-responsive- ness so that inflammation does not develop in relation to ordinarily harmless exposure to mucosal antigens. In contrast, in individuals with inflammatory bowel diseases, Crohn’s disease, the mucosal response set point is shifted toward responsiveness and we have the development of inflammation. Evidence in favor of this view is inherent in the recent finding that in Crohn’s disease, just as in TNBS- colitis, there is heightened reactivity to one’s own bacterial microflora and thus a loss of tolerance to these mucosal constituents. Future study will be focused on defining the precise mechanisms that determine the all-important mucosal response set point, the genetically-determined factors that determine whether or not tolerogenic responses or immunogenic response in the mucosa will be dominant.

Such studies will help to define the fundamental factors which determine why some individuals develop Crohn’s disease and others do not.

Meanwhile, work must go forward directed at attempts to treat Crohn's disease by addressing the outcome of these funda- mental abnormalities, the Thl T cell final common pathway.

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