IL-12 and T-lymphocyte dependant mucosal immune respons

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Chapter 7

Summary and concluding remarks
Summary

The immune system is a first line of defense against pathogens or other foreign luminal pathogens, but itself may be a cause of disease by reacting to self-components (autoimmunity), by mounting a response to non-pathogenic antigens or by causing an exaggerated immune response (hypersensitivity). Although the specific aetiology of Crohn’s disease remains unknown, an abnormal T cell activation plays a central role in the pathogenesis of this inflammatory bowel disease.

Chapter 1 describes the pathophysiology of Crohn’s disease (1.1), focusing on the role of intestinal T lymphocytes and the production of pro-inflammatory cytokines. The initiation of a Th-1 cell mediated response (1.2) is described with focusing on the Th1-driven cytokines, i.e. IL-12 and IL-18. The mucosal immune system in the gastrointestinal tract (the so-called gut associated lymphoid tissue) is somewhat different from the systemic immune system. Mucosal T lymphocyte trafficking (1.3) is described by elucidating the different pattern of migration of naïve versus memory effector T lymphocytes. Current knowledge indicates IL-12, TNF-α and IFN-γ as major key cytokines involved in maintaining a chronic Th1-cell response (1.4). We discussed the regulatory mechanisms of the T-cell immune response (1.5) and in particular we focused on the anti-inflammatory properties of IFN-γ (1.6) and NO during T-cell responses (1.7). Finally, we summarised the three main experimental models of T-cell response in mice (1.8).

In chapter 2, we investigated the expression of IFN-γ and IL-4, considered respectively the prototypic Th1- and Th2-type cytokines, in intestinal specimens from patients with either Crohn’s disease or ulcerative colitis (the other form of inflammatory bowel disease) and from controls. We found increased number of IFN-γ-positive cells in the lamina propria of Crohn’s disease as compared to both ulcerative colitis and controls, confirming that in Crohn’s disease the type of T-cell response is Th1-mediated.

In chapter 3, the colitis model induced by administration of 2,4,6-trinitrobenzene sulfonic acid (TNBS) was used to study the mucosal T-cell response. We found that reactive T lymphocytes in TNBS-induced colitis are recruited in the lamina propria via expression of the gut homing α4β7, and that local inflammation caused a generalized infiltration of the gut associated lymphoid tissue by memory T lymphocytes.

IL-12 is considered a major cytokine in driving the Th1-cell response. In chapter 4, the T-cell response was investigated in the total absence of IL-12 (in IL-12p40-deficient mice) and in
the presence of endogenous p40 (IL-12p35-deficient mice still produce p40). We showed that IL-12p40-/- mice developed severe colitis and expressed high levels of mucosal IL-18 mRNA while TNBS-IL-12p35-/- mice developed only a mild colitis and showed low levels of mucosal IL-18 mRNA. Anti-p40 treatment dramatically increased disease in TNBS-IL-12p35-/- mice, indicating that endogenous IL-12p40 has a (agonistic) biological role independently from IL12p70, which is protective in TNBS-induced colitis.

IFN-γ is a pro-inflammatory cytokine involved in Crohn’s disease. In chapter 5, mice lacking the α-chain of the IFN-γ receptor (IFN-γR1-deficient mice) and therefore unable to respond to IFN-γ were studied after induction of TNBS-colitis. We showed that IFN-γ is not necessary for the development of TNBS-induced colitis that was marked by greater number of intestinal cells, represented by macrophages and CD4⁺ T cells and increased production of Th1 cytokines. Surprisingly, intestinal macrophages were positive for IFN-γ and therefore may contribute to IFN-γ production in inflammatory responses in mice.

In chapter 6, the anti-inflammatory properties of IFN-γ were re-examined in mice lacking either IFN-γ or IFN-γ receptor. In the absence of IFN-γ, these mice showed increased lymphocyte proliferation in the germinal centers of colonic lymphoid follicles after induction of colitis. Lack of IFN-γ was associated with a defective apoptosis that was not related to a defect of iNOS induction, but to the reduced caspase-3 activation.

Concluding remarks

In the present study we were able to investigate the role of endogenous IL-12 (in IL-12p40-/- mice), IL-12p40 (in IL-12p35-/- mice) and IFN-γ (in IFN-γR1-/- mice) during the induction of a Th1-mediated model of colitis. Firstly, colitis was still induced in the absence of IL-12p70, probably because of a compensatory role of IL-18. Secondly, we showed that endogenous p40 has a biologic (agonistic) activity different from IL12p70 that may contribute to maintain mucosal homeostasis. Currently, pharmaceutical companies are developing anti-IL-12p40 neutralizing antibodies for the treatment of Crohn’s disease and rheumatoid arthritis. By generating anti-IL-12 treatment in Crohn’s disease, IL-12p70 or IL-12p35 should be specifically inhibited without down-regulating endogenous IL-12p40. Thirdly, and in contrast to the current opinion, IFN-γ was not absolutely required for the induction of Th1-mediated colitis and we provided evidence that IFN-γ is needed to counteract T-lymphocyte
proliferation and to induce apoptosis (cell death) of Th1-lymphocytes. Thus, the biological role for IFN-γ is more complex than we expected: IFN-γ not only acts as pro-inflammatory cytokine but it also possesses important immunoregulatory activities.