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Review

Experimental colitis models: Insights into the pathogenesis of inflammatory bowel disease and translational issues

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ABSTRACT

Inflammatory bowel diseases, ulcerative colitis and Crohn's disease are characterized by chronic relapsing inflammation of the gastrointestinal tract of unknown etiology that seems to be the consequence of a genetically driven dysregulated immune response against various local and environmental triggers through a defective epithelial barrier. During the last decades, a large number of animal experimental models of intestinal inflammation have been generated and provided valuable insights into the mechanisms that either maintain mucosal homeostasis or drive intestinal inflammation. Their study enabled the identification of various treatment targets and the development a large pipeline of new drugs, mostly biologics. Safety and therapeutic efficacy of these agents have been evaluated in a large number of clinical trials but only a minority has reached the clinic so far. Translational successes but mostly translational failures have prompted to re-evaluate results of efficacy and safety generated by pre-clinical testing and to re-examine the way to interpret experimental *in vivo* data. This review examines the contribution of the most popular experimental colitis models to our understanding of the pathogenesis of human inflammatory bowel diseases and their translational input in drug development and discusses ways to improve translational outcome.

Contents

1. Introduction

Inflammatory bowel disease (IBD) comprises of two separate clinical entities ulcerative colitis (UC) and Crohn's disease (CD). Both are characterized by chronic relapsing inflammation of the gastrointestinal tract of unknown etiology. The principal hypothesis for their pathogenesis is that intestinal inflammation represents the end result of a genetically driven dysregulated immune response against antigens of the intestinal microflora though a

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Table 1
Experimental models of IBD.

Epithelial barrier defects	**Aberrant adaptive T cell responses**
DSS (Okayasu et al., 1990)	***Excessive effector cell responses***
N-cadherin dominant negative (Hermiston and Gordon, 1995)	TNBS[a] (Neurath et al., 1995)
Muc1/2$^{-/-}$ (Nishida et al., 2012; Van der Sluis et al., 2006)	Oxazolone[a] (Boirivant et al., 1998)
Mdr1a$^{-/-}$ (Panwala et al., 1998)	TNF$^{\Delta ARE}$ (Kontoyiannis et al., 1999)
Innate immunity defects	STAT4 tg (Wirtz et al., 1999)
A20$^{-/-}$ (Lee et al., 2000)	TCRα$^{-/-}$ (Mizoguchi et al., 1996)
STAT3$^{-/-}$ (Takeda et al., 1999)	***Regulatory and effector T cell imbalance***
CD40 mAb→*RAG*$^{-/-}$ (Uhlig et al., 2006)	CD45RB^{high} adoptive transfer (Powrie et al., 1993)
Helicobacter hepaticus→SCID/*RAG*$^{-/-}$ (Li et al., 1998)	IL-2$^{-/-}$ (Willerford et al., 1995)
IEC/IKK-γ$^{-/-}$ (Nenci et al., 2007)	TGFβ1$^{-/-}$ (Shull et al., 1992)
TRUC (Garrett et al., 2007)	IL-10$^{-/-}$ (Berg et al., 1996)
Spontaneous colitis models	Gαi2$^{-/-}$ (Rudolph et al., 1995)
C3H/HeJBir (Mahler et al., 1998)	Tgε26 (Hollander et al., 1995)
SAMP1/Yit(Fc) (Kosiewicz et al., 2001)	TGFβRII DN (Gorelik and Flavell, 2000)

[a] Can also be categorized to experimental colitis associated with epithelial barrier defects as disruption of the epithelial barrier with ethanol is necessary for the development of intestinal inflammation.

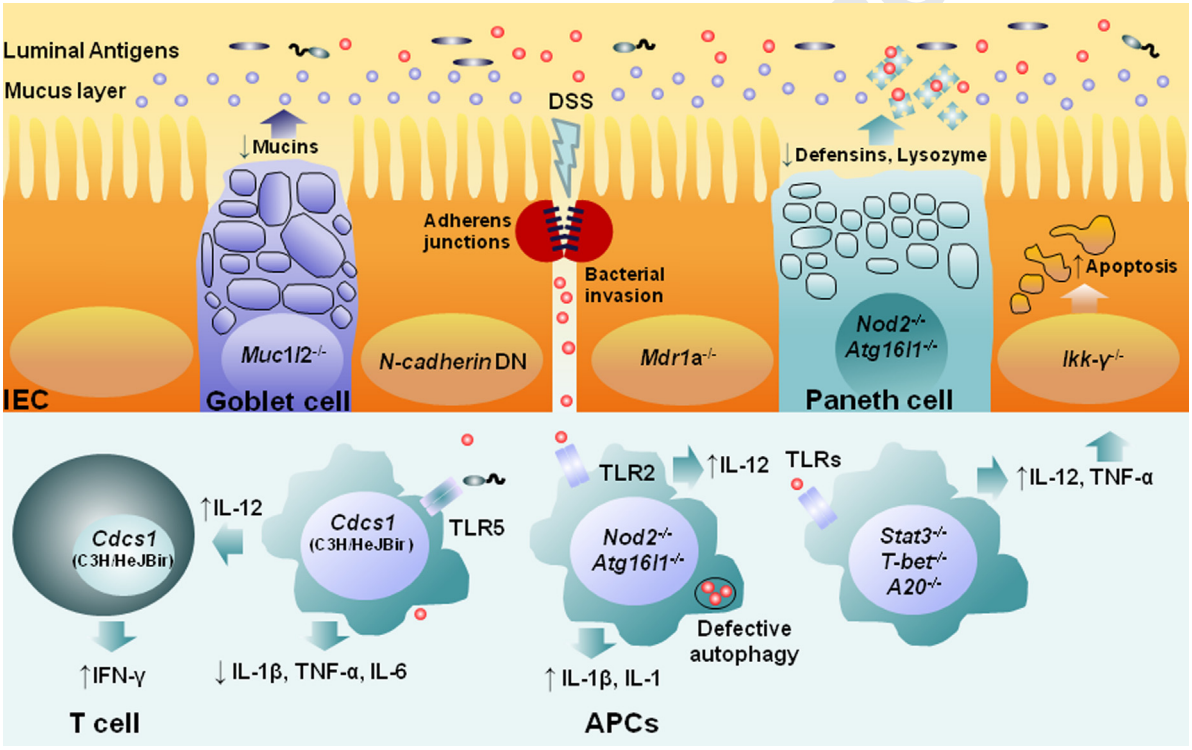

Fig. 1. Experimental colitis models with epithelial barrier and innate immunity defects. Chemical disruption of the epithelial barrier, deletion of genes related to the formation of adherent junctions and inadequate production of mucin, defensins and lysozyme by the epithelium result to bacterial invasion. Loss of immunoregulation, aberrant microbial sensing by pattern recognition receptors and poor microbial handling due to defective autophagy lead to up-regulation of pro-inflammatory mediators by innate immune cells and chronic intestinal inflammation. APC: Antigen Presenting Cell, *Atg16l1*: Autophagy related 16l1, DN: Dominant negative, DSS: Dextran Sulfate Sodium, IEC: Intestinal Epithelial Cell, IFN-γ: Interferon-γ, *Ikk-γ*: IκB kinase-γ, IL-1β: Interleukin 1β, *Mdr1a*: Multiple Drug Resistance 1a, *Nod2*: Nucleotide-Binding Oligomerization Domain 2, *Stat3*: Signal Transducer and Activator of Transcription, TLR: Toll-like Receptor, TNF-α: Tumor Necrosis Factor-a.

defective epithelial barrier and under the influence of various environmental triggers.(Abraham and Cho, 2009) A significant amount of data to support this hypothesis has been generated by studies in experimental models of intestinal inflammation. Since the description of the first such model by Kirsner and Elchlepp (1957) almost 60 years ago, more than 50 different murine models have been generated by genetic engineering guided partly by human genome wide association studies in IBD (Kirsner and Elchlepp, 1957). In the following years, murine experimental colitis models have helped to identify the key elements of mucosal immune homeostasis such as the integrity of the epithelial barrier, the dynamic innate immune responses and the tight regulation of adaptive immune responses. The purpose of this review is to present the most popular experimental colitis models (Table 1), to describe their contribution to our understanding of human IBD pathogenesis, and to discuss their translational implication for the treatment of the human condition.

2. Experimental colitis models with epithelial barrier defects

There is accumulating evidence that epithelial barrier dysfunction participates in IBD pathogenesis (Fig. 1). Strong support for such a mechanism comes from animal models of experimental colitis as chemical disruption or genetic defects in epithelial barrier components result to intestinal inflammation. Administration of

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