Immunobiology 220 (2015) 227–235

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Review

Perturbations of mucosal homeostasis through interactions of intestinal microbes with myeloid cells

Regina Schey[a,*], Claudia Danzer[a], Jochen Mattner[a,b,*]

[a] Mikrobiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene, Universitätsklinikum Erlangen and Friedrich-Alexander Universität Erlangen-Nürnberg, D-91054 Erlangen, Germany
[b] Division of Immunobiology, Cincinnati Children's Hospital, Cincinnati, OH 45229, USA

ARTICLE INFO

Article history:
Received 1 May 2014
Received in revised form
20 November 2014
Accepted 21 November 2014
Available online 22 November 2014

Keywords:
Inflammatory bowel disease
Intestinal microbiota
Mucosal tolerance
Myeloid cells
Surface molecules

ABSTRACT

Mucosal surfaces represent the largest areas of interactions of the host with its environment. Subsequently, the mucosal immune system has evolved complex strategies to maintain the integrity of the host by inducing protective immune responses against pathogenic and tolerance against dietary and commensal microbial antigens within the broad range of molecules the intestinal epithelium is exposed to. Among many other specialized cell subsets, myeloid cell populations – due to their strategic location in the subepithelial lamina propria – are the first ones to scavenge and process these intestinal antigens and to send consecutive signals to other immune and non-immune cell subsets. Thus, myeloid cell populations represent attractive targets for clinical intervention in chronic inflammatory bowel diseases (IBDs) such as ulcerative colitis (UC) and Crohn's disease (CD) as they initiate and modulate inflammatory or regulatory immune response and shape the intestinal T cell pool. Here, we discuss the interactions of the intestinal microbiota with dendritic cell and macrophage populations and review in this context the literature on four promising candidate molecules that are critical for the induction and maintenance of intestinal homeostasis on the one hand, but also for the initiation and propagation of chronic intestinal inflammation on the other.

Contents

Abbreviations: CD, Crohn's disease; DC, dendritic cell; IBD, inflammatory bowel disease; TLA1, TNF-like factor 1A; TREM-1, Triggering receptor expressed on myeloid cells-1; UC, ulcerative colitis.

* Corresponding authors at: Mikrobiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene, Universitätsklinikum Erlangen and Friedrich-Alexander Universität Erlangen-Nürnberg, Wasserturmstr. 3/5, D-91054 Erlangen, Germany. Tel.: +49 09131 8523640; fax: +49 09131 85 1001.
E-mail addresses: Regina.Schey@uk-erlangen.de (R. Schey), Jochen.Mattner@uk-erlangen.de (J. Mattner).

http://dx.doi.org/10.1016/j.imbio.2014.11.014
0171-2985/

Introduction

The intestine is continuously exposed to various different antigens, which originate from dietary and commensal microbial sources. While the mucosal immune system has to act tolerogenic against those, it needs to protect the host against invading pathogens. Thus, the mechanisms underlying the balance between pro- and anti-inflammatory processes in the gut require distinct cellular and soluble mediators. The distinct cell populations that contribute to the maintenance of the integrity of the mucosal barrier include goblet cells, paneth cells, M cells, enteroendocrine cells, enterocytes and various different specialized immune cells (Garrett et al., 2010) including innate and adaptive lymphocytes (Pearson et al., 2012), macrophages, conventional CD11c^{hi} dendritic cells (DCs) and plasmacytoid DCs (pDCs) (Iwasaki, 2007; Smith et al., 2005) with the latter three ones being the main focus of this review. These different immune cell populations reside within distinct locations in the gut associated lymphoid tissue (GALT) and the subepithelial lamina propria (Varol et al., 2010) and express a broad range of immune receptors in order to immediately activate and shape the immune response. Among those are toll-like receptors (TLRs), Scavenger receptors (SR) and C-type lectin receptors (Gordon, 2002), but also T and B cell receptors. Upon activation of these receptors, potent immune modulatory functions are unleashed, such as the release of a broad range of different soluble and membrane-bound mediators. These include, for example, cytokines such as IL-17 and IL-22 released by Th17 cells (Harrington et al., 2005) or group 3 innate lymphoid cells (ILC3) (Cella et al., 2009; Cupedo et al., 2009; Luci et al., 2009; Sanos et al., 2009; Satoh-Takayama et al., 2008; Takatori et al., 2009), defensins secreted by epithelial cells (Zhao et al., 1996) and membrane-bound TNF-like cytokines such as the B cell activating factor BAFF expressed on T cells (Schneider et al., 1999), monocytes, macrophages and DCs (Nardelli et al., 2001; Shu et al., 1999) or the proliferation inducing ligand APRIL, highly expressed on peripheral blood leukocytes (Kelly et al., 2000) (Shu et al., 1999).

Recognition of intestinal bacteria

The release of these different compounds is initiated upon ligation of different innate and adaptive immune receptors. Dependent on the receptor(s) engaged, inflammatory or tolerogenic immune responses can be generated. This complex network is required for the regulation of the intestinal immune homeostasis on a molecular and cellular level that needs to mount inflammatory immune responses against pathogens, but also is required for the maintenance of tolerance against the physiological intestinal microbial flora. Thus, in order to maintain intestinal homeostasis, microbial signals are continuously sensed by intestinal epithelial cells (Nenci et al., 2007; Zaph et al., 2007). Despite serving as a physiological barrier, the disruption of the intestinal epithelial layer can lead to the translocation of intestinal microorganisms and the activation of different receptors on subepithelial immune cell subsets. Distinct, highly conserved pathogen-associated molecular patterns (PAMPs) of microbes as diverse as bacteria, fungi or viruses, for example, are thereby recognized by relatively few TLRs (Rakoff-Nahoum et al., 2004; Blasius and Beutler, 2010). However, single receptors within the TLR family are able to distinguish between different formations of the same microbial ligand. Gram-negative bacteria, for example, differ in the structure of their lipopolysaccharides (LPS) in the outer membrane, namely the lipid A structure, the core sugars, the O-polysaccharide chain and the O-antigen repeats (Raetz, 1990). The divergent recognition of these different, species-specific LPS structures leads to alterations in TLR4-activation, and subsequently to changes in the recruitment of signaling components, in the release of cytokines and/or chemokines and in the expression of costimulatory and/or adhesion molecules (Beutler, 2000; Freudenberg et al., 2008; Jerala, 2007). However, bacterial ligands such as the zwitterionic polysaccharide A (PSA) from *Bacteroides fragilis* exhibit even dual functions without apparent formation changes: on the one hand PSA serves as major pathogenic factor for *B. fragilis* as PSA is critical for bacterial growth and the formation of intra-abdominal abscesses (Surana and Kasper, 2012), which is at least partially dependent on TLR 2 (Wang et al., 2006). PSA-dependent TLR2-engagement induces also the production of TNF-α and iNOS as well as the expression of MHC II. The subsequent presentation of PSA by MHC II on antigen presenting cells activates CD4+ T cells to secrete IFN-γ (Wang et al., 2006). On the other hand, PSA directs potent anti-inflammatory responses through the engagement of TLR2, mainly through the subsequent production of IL-10, which exhibits potent macrophage-deactivating and anti-inflammatory effects (Bogdan et al., 1991) and regulates the growth, function and/or differentiation of multiple cell populations (Moore et al., 2001) including Tregs (Murai et al., 2009). Allelic variations within the *il-10* or the *il-10r* gene are closely associated with susceptibility to IBD (Kaser et al., 2010) and mice that are deficient in either IL-10 or the IL-10R2 develop severe enterocolitis (Berg et al., 1995; Kuhn et al., 1993; Spencer et al., 1998). A recent study highlighted thereby the critical protective role of IL-10R expression on macrophages (Zigmond et al., 2014). Thus, IL-10 plays a substantial role in the maintenance of intestinal homeostasis and the PSA induced T cell-dependent IL-10-production under steady state conditions in the intestinal tract might reflect a protective probiotic effect in this context (Round et al., 2011). Furthermore, peritoneal macrophages can release IL-10 upon exposure to *B. fragilis* (Cohen-Poradosu et al., 2011).

Thus, on the one hand it has been well established that bacterial compounds can shape the extent and phenotype of an ongoing immune response. On the other hand, however, it has not been investigated in great detail so far whether polymorphisms within the genes encoding the different innate immune receptors influence the microbial composition of the gut and subsequently the balance between inflammation and mucosal tolerance.

Intestinal microbiota

The identification of different microbial species that densely populate the intestine and the characterization of distinct bacterial colonization clusters have evolved as central research focus within recent years. Although bacterial species themselves vary extensively among individuals, the intestinal bacterial composition exhibits similarities within the respective intestine-populating bacterial families (Turnbaugh et al., 2009). The main bacterial phyla present in the gut flora are *Firmicutes* (95% *Clostridia*) and *Bacteroides* (Eckburg et al., 2005; Suau et al., 1999). In contrast, the phyla *Proteobacteria, Actinobacteria, Fusobacteria* and *Verrucomicrobia* are scarce (Eckburg et al., 2005).

The majority of intestinal microbes consists of commensal bacteria that provide benefits for the host, including the degradation of nutrients and various defense mechanisms against pathogenic organisms (reviewed in Shanahan, 2002). One of those, the gut flora-mediated colonization resistance, however, can be disrupted during antibiotic treatment allowing the outgrowth of diarrhea-causing agents such as *Salmonella species* or *Clostridium difficile* (Spencer, 1998). *Vice versa*, fecal transplants reconstituting the physiological microbial flora in the gut proved to be effective for the treatment of – otherwise even refractory – *C. difficile* infections (van Nood et al., 2013). In particular, *Clostridium scindens*, a bile-acid 7α-dehydroxylating intestinal bacterium, has been recently associated with resistance to *C. difficile* infections (Buffie et al., 2014).