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Microbiome, pattern recognition receptor function in health and inflammation

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ABSTRACT

The innate immune system plays an important role in shaping the microbiota into configurations that are tolerated and beneficial to the host, thereby playing a crucial role in human health. Innate immunity is based on the fundamental principle that Pattern Recognition Receptors (PRRs) recognise pathogen associated molecular patterns as non-self-entities and trigger intracellular signalling pathways that lead to the induction of numerous cytokines and chemokines that help maintain host resistance to infections. Dysregulation of this interaction has been identified as the core defect that leads to chronic intestinal inflammation allowing certain microbiota to be harmful to host health. This dysbiosis of the microbiome is found associated with numerous chronic diseases. A logical explanation would be that genetic defects in the recognition and response pathways that the host uses to identify these microbial pathogens could lead to altered microbial colonisation or mis-recognition of normal bacteria leading to diseases. The interaction between pattern recognition receptors, microbial traits and human health with respect to the gut are now rapidly resolved and will be the subject of this review.

" We are not just on 'friendly' terms with our gut bacteria - the relationship is infinitely more intimate that that - we are married to them" - Katrina Ray [1]

Introduction

All mammals live in close association with their surrounding microbes. The colonisation of the mammalian gut starts at birth and continues over its life time by a succession of microbial consortia. The composition of these microbial communities is dictated by changes in diet and life events [2,3]. The human gut supports one of the most diverse microbial ecosystems on the planet, with at least 100 trillion microbial cells comprising thousands of microbial species [4]. This collection of microbes harboured within and on us constitute our **microbiota** while the genes that they encode is termed as the **microbiome** [5]. Efforts to identify the composition and role of bacteria that are part of this microbiota has been hampered as only a small minority of these can be cultured. Also, the roles of viruses, archaea and other eukaryotes within this community are less well known. However, recent advances in high throughput sequencing has enabled us to circumvent the need to culture these microbes contributing to the rapid expansion in our knowledge of their repertoire within the last ten years [6].

The knowledge that a healthy gut is important in maintaining human health has been recognised since the time of Hippocrates. This homeostasis is maintained by symbiotic microbes which provide the host with essential nutrients along with carrying out various metabolic functions such as the fermentation and absorption of indigestible compounds [5,7]. Thus, our microbiota can be considered to have metabolic activity equivalent to an organ and is thus sometimes referred to as the 'neglected organ' [8]. In addition to the metabolic benefits, our microbiota also contributes to the defence against colonisation by opportunistic pathogens by competing with them and preventing their propagation. Crucially, our gut microbiota also contributes to the development and maintenance of the intestinal epithelial barrier [9] and interacts with the immune system promoting the maturation of immune cells and proper development of immune functions [10].

Our body hosts trillions of bacteria so how do our bodies

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maintain this symbiosis without eliciting immune responses against them that could lead to exaggerated organism-wide inflammation and wide-ranging damage? Research carried out in the last twenty years has been pivotal in understanding this host-microbial interaction. One of the major discoveries has been the identification of pattern recognition receptors (PRR), important components of the innate immune system that sense microbes through conserved molecular structures called pathogen associated molecular patterns (PAMPs) [11]. Despite the continuous exposure to these PAMPs, commensal microbes do not normally initiate inflammatory responses, they instead promote the development and enhance host immune function [12]. An important paradigm shift has been in understanding how these molecules and receptors are able to achieve such opposing responses between pathogens and symbionts. The context in which the host receives PAMP signals dictates the strength of the immune response. For instance, during infections, PAMP signals will be received in the presence of cell damage and cytosolic detection of PAMPs would result in inflammation (Fig. 1A). On the other hand, symbiotic microbiota usually do not harm the host cells and the PAMPs appear to directly promote beneficial outcomes (Fig. 1B–D) [13,14].

PAMPs are recognised by Pattern Recognition Receptors (PRRs) and several families of PRRs have been identified which are found expressed in various compartments within the cell. These include the Toll-like receptors (TLRs), the nucleotide-binding oligomerisation (NOD) – like receptors (NLRs), the RIG-I-like receptors, the C-type lectin receptors, the absent in melanoma 2 (AIM2)-like receptors and the OAS like receptors [15]. These receptors are responsible for continuously monitoring the presence of microorganisms within tissue.

Innate immunity is based on the fundamental principle that PRRs recognise PAMPs as non-self-entities and trigger intracellular signalling pathways that lead to the induction of numerous cytokines and chemokines that help maintain host resistance to infections [16]. Ironically though, in its zeal to defend the host, aberrant recognition of commensal bacteria as foreign leads to a persistently activated innate immune response which harms the host contributing to various inflammatory disorders including artherosclerosis, meningitis, systemic lupus erythematosus, hepatitis and Inflammatory Bowel Disease (IBD). The interaction between PRR and PAMPs has been an important area of study in IBD with a number of pathways being identified as abnormal and highlighting potential avenues for intervention (Table 1).

The purpose of this review is to discuss the interaction between pattern recognition receptors, microbial traits and human health using IBD as an example.

IBD

The innate immune system plays an important role in shaping the microbiota into configurations that are tolerated and beneficial to the host, thereby playing a crucial role in human health. Dysregulation of this interaction has been identified as the core defect that leads to chronic intestinal inflammation allowing certain

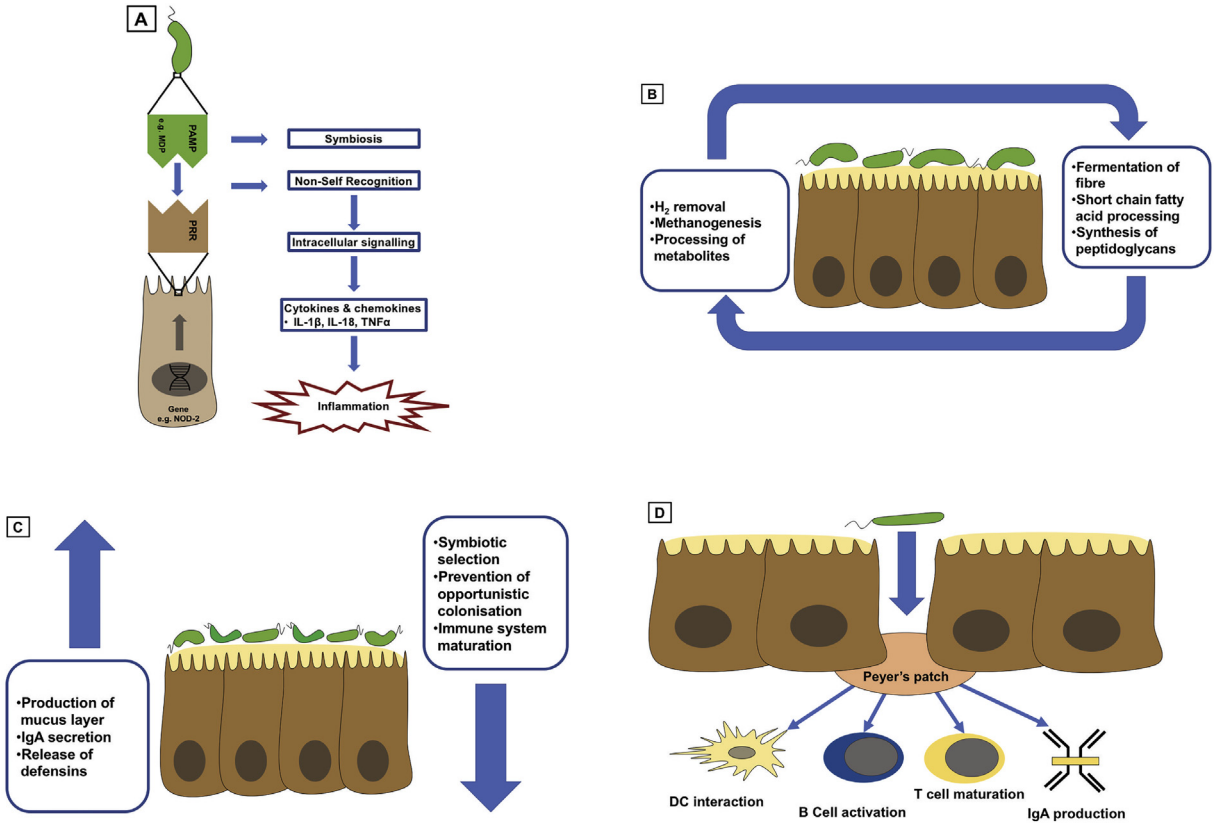

Fig. 1. **(A)** An overview of Pattern Recognition Receptor (PRR) – Pathogen Associated Molecular Pattern (PAMP) interaction in health (symbiotic response to commensal bacteria) and Inflammatory Bowel Disease (e.g. defect in NOD-2 pathway). **(B)** Symbiotic role of microbiome in intestinal metabolic functions. **(C)** Overview of the importance of microbiome in epithelial barrier development and maintenance. **(D)** Schematic of the function of symbiotic microbiota in intestinal immune interaction and development of tolerance.