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Review

Microbiota, immunity and the liver

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ABSTRACT

The gut harbors a complex community of over 100 trillion microbial cells known to exist in symbiotic harmony with the host influencing human physiology, metabolism, nutrition and immune function. It is now widely accepted that perturbations of this close partnership results in the pathogenesis of several major diseases with increasing evidence highlighting their role outside of the intestinal tract. The intimate proximity and circulatory loop of the liver and the gut has attracted significant attention regarding the role of the microbiota in the development and progression of liver disease. Here we give an overview of the interaction between the microbiota and the immune system and focus on their convincing role in both the propagation and treatment of liver disease.

Contents

Abbreviations: GALT, gut associated lymphoid tissues; ILF, isolated lymphoid follicle; LTi, lymphoid tissue inducers; Th, T helper; RORγt, Retinoid related orphan receptor gamma t; IL, interleukin; MAMP, microbe associated molecular pattern; LPS, lipopolysaccharide; PRR, pattern recognition receptor; TLR, toll-like receptor; NOD, nucleotide-binding oligomerisation domain; DSS, dextran sulphate sodium; sIgA, secretory immunoglobulin A; PPAR-γ, Peroxisome proliferator-activated receptor gamma; SFB, single filamentous bacteria; TGF-β, transforming growth factor beta; ATP, adenosine triphosphate; FOXP3, forkhead box P3; PSA, polysaccharide A; SCFA, short chain fatty acid; BAFF, B cell activating factor; APRIL, a proliferation-inducing ligand; CV, conventional; SPF, specific pathogen free; ALD, alcoholic liver disease; TNF-α, tumor necrosis factor alpha; NAFLD, non alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma.

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1. Introduction

The microbiota consists of complex communities of microorganisms, which populate the skin and mucosal tissues throughout the body, forming a nourished ecosystem within its host. Thousands of years of microbial and immune co-evolution have led to a harmonious co-existence between the host and its colonizing microbes shaping the repertoire of both the host's immune system and microbiota reciprocally [1].

The dynamic interaction between the host and its microbiota is most clearly demonstrated in the gastrointestinal tract where the microbiota populates at an astounding density. The human gastrointestinal tract hosts over 100 trillion microbes, predominantly consisting of bacterial species, although archaeal and eukaryotic species are also represented. The total number of resident microbes exists at around ten times the number of cells in the human body and the collective genome of the microbiota is around 150-fold larger than that of our own. This ecosystem is dominated by four major phyla: Firmicutes, Bacteroidetes, Actinobacter and Proteobacter in order of abundance. However, with only around one-tenth of the total colonizing bacterial species represented in each individual, the potential for variation in microbial composition from one human to another is infinite whereby each individual is assigned their own microbial signature [2]. Despite this, an individual's microbial make-up is by no means fixed, instead forming an adaptive community in conjunction with the current corporal environment [3]. In line with this, courses of antibiotic treatment, spells of acute diarrheal illness and dietary modifications of a high fiber diet have been shown to alter gut microbial densities and populations [4]. Notwithstanding the limitless potential for inter/intra-individual variability, 16S RNA sequencing has directed the definition of a microbial 'core', reporting 66 species conserved in over 50% of the population, yet still, the majority of units were found to be individual specific [5].

A healthy human gastrointestinal tract represents a stable, warm and nutrient rich environment at homeostasis. In the mutualistic interest of survival, the colonizing microbiota ensures the preservation of the host's health, allowing for the configuration of a stable microbial ecosystem. In parallel, the host benefits from the growth of a metabolically active population whose presence not only provides essential nutrients, but also assists digestion, through the fermentation of complex carbohydrates, ensuring optimal nutritional procurement. Furthermore, establishment of the gut microbiota provides inherent competition against potential pathogens, limiting the resources, access and physiological space available to any foreign invaders [6].

Despite this apparent alliance between the gut microbiota and its host, the sheer number and intimate association of the two poses a perpetual threat to the host's health that requires constant supervision.

As such, the role of the individual's immune system in fine-tuning and shaping the microbiota is of paramount importance, with a stable gut ecological system poised around regulatory activity elicited by the human immune system with concurrent education from its colonizing microbes.

Whilst the importance of gut microbiota and its influence on intestinal health has been widely documented, it is now apparent that the role of microbiota can be extrapolated to health and disease beyond that of the intestinal tract.

One of the primary organs in close association with the gastrointestinal tract is the liver. Venous blood flow from the gut reaches the liver via the portal vein, carrying with it products of gut flora and of host's immunological responses to these organisms. Concurrently, the liver produces bile that flows to the gut directly influencing the resident microbial environment. This circulatory loop between the liver and gut explains how changes to the gut flora can have both beneficial and harmful consequences, the latter case potentially playing a role in the pathogenesis of liver diseases [7,8], the study of which may allow for the translation of personalized preventative and therapeutic strategies.

This article reviews the current knowledge on the role of the microbiota and immunity in liver disease and its progression. Here, we unpick the reciprocal regulation of host homeostasis through its immune system and gut microbiota. These insights help to explain disease pathogenesis when this delicate relationship falls apart.

2. Birth of the microbiota

The sterile environment of the uterus denotes that we begin life devoid of microbiota with primary microbial colonization occurring at parturition. However, recently there have been reports of *in utero* exposure to maternal bacteria/bacterial components, with microbes detected in the placenta, meconium and amniotic fluid suggesting colonization prior to birth [9–12], yet this remains to be fully elucidated.

Nevertheless, the greatest influence on the development and establishment of the gut microbiota arises from maternal vertical transmission at birth. The initial microbial settlers consist of a limited and unstable repertoire amenable to change in order for the evolution of a stable ecosystem. Pioneering species can vary dependent on the method of delivery. Neonates are normally colonized by bacteria derived from the mother's vaginal commensals, principally *Lactobacillus* and *Prevotella* species, whereas neonates delivered by caesarean section are predominantly inoculated with skin commensals, consisting primarily of *Staphylococcus* and *Corynebacterium* species [13,14]. As a result, caesarean section born neonates acquire dominant bacterial divisions, Firmicutes and Bacteroidetes, at a later stage than those born transvaginally. On the other hand, infants born transvaginally lag behind caesarean-section born infants in the exposure and in turn, colonization by skin and oral microbiota [15].

Microbial succession is determined significantly by the primary colonizing species, transforming a previously unadulterated ecosystem in a way that entices the successive colonization of microbes suited to the novel environment. The newborn gut has high oxygen levels and as a result is inoculated early on with facultative anaerobes, especially *Escherichia coli*. These pioneering species subsequently decrease the oxygen levels in the gut driving ensuing colonization of strict anaerobes including *Clostridium* and *Bacteroides* species [16]. The first year of neonatal life frames the critical window, shaping the composition of the