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Review

Immune and genetic gardening of the intestinal microbiome

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ABSTRACT

The mucosal immune system – consisting of adaptive and innate immune cells as well as the epithelium – is profoundly influenced by its microbial environment. There is now growing evidence that the converse is also true, that the immune system shapes the composition of the intestinal microbiome. During conditions of health, this bidirectional interaction achieves a homeostasis in which inappropriate immune responses to non-pathogenic microbes are averted and immune activity suppresses blooms of potentially pathogenic microbes (pathobionts). Genetic alteration in immune/epithelial function can affect host gardening of the intestinal microbiome, contributing to the diversity of intestinal microbiota within a population and in some cases allowing for unfavorable microbial ecologies (dysbiosis) that confer disease susceptibility.

1. Introduction

The small intestine and colon house a complex bacterial ecosystem consisting of an estimated 10^{14} cells in humans, 10-fold greater than the number of human cells [1]. Many have beneficial functions such as harvesting energy from otherwise indigestible plant polysaccharides (transferred to the host via short chain fatty acids), triggering formation of an intestinal mucus barrier, promoting intestinal vascularization, metabolizing xenobiotics, and preventing colonization by pathogens [2–6]. The microbiome also has profound effects on the immune system, the subject of other reviews in this issue. The beneficial properties of the intestinal microbiome confer an evolutionary advantage to animals that can regulate the microbial communities in their digestive tracts. Intestinal microbes also benefit from the survival and reproduction of their hosts. It has been hypothesized that in response to evolutionary pressure favoring mutual survival, hosts and intestinal microbes have co-evolved traits that foster symbiosis [7,8].

The existence of genetically encoded mechanisms for regulating microbial composition is suggested by the observation that across mammals, the intestinal microbiome clusters by taxonomic order rather than geography [9]. This could also reflect similarities in diet, which has been shown across mammals and within human populations to strongly influence the intestinal microbiome [10–12]. However, the microbiome of taxonomic groups such as bears/pandas with highly variable diets (carnivore, omnivore, herbivore) most resembles the microbiome of other members of the same taxonomic group rather than taxonomically unrelated mammals with a similar diet [9]. An alternate non-genetic explanation for taxonomic clustering of microbiota is a founder effect due to initial colonization by microbes of parental origin, allowing for stable transmission of a species-specific microbiome without active host involvement. Human neonates are known to be initially colonized by maternal vaginal or skin bacteria depending on mode of delivery and founder effects have been demonstrated for specific microbes such as *Helicobacter pylori* [13,14]. However, longitudinal studies of human infants and ex-germ-free mice have demonstrated wide fluctuations in microbial community structure – possibly reflecting environmental or stochastic factors – before

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Table 1
Genes that have been implicated in microbial gardening in mouse and/or human studies. Targets of microbial gardening are more abundant in KO mice except where noted. D = depleted, I = mucosal invasion, A = altered abundance that was not further described (or phylotypes within the taxonomic group were both increased and decreased).

Gardening gene	Putative microbial targets of gardening	Phenotype of knockout mice	Disease association (for human genetic variants)
Pattern recognition receptors			
MyD88 [20]	Rikenellaceae, Porphyromonadaceae		
MyD88, epithelium [21]	TM7, *Lactobacillus* (D), *Klebsiella pneumonia* (I)	Exacerbated DSS colitis	
TLR5 [23,25]	*Escherichia coli* (I), Prevotellaceae (A), Lachnospiraceae (A), *Alistipes* (A), *Bacteroides* (A)	[b]Obesity, spontaneous colitis	
[a]TLR2 [26]	*Alistipes*, *Lactobacillus*, *Clostridium*, *Eubacterium*	Protection from diet-induced metabolic syndrome	
NOD2 [31–34]	Proteobacteria, Bacillus, Clostridium group IV	[b]Exacerbated DSS colitis	Crohn's disease, Blau syndrome
[a]RIP2 [31]		[b]Exacerbated DSS colitis	
[a]NLRP6 [38]	*Prevotellaceae*, TM7	[b]Exacerbated DSS colitis	
[a]ASC [38]	*Prevotellaceae*, TM7	[b]Exacerbated DSS colitis	
[a]Caspase-1 [38]	*Prevotellaceae*, TM7	[b]Exacerbated DSS colitis	
Epithelium			
[a]IL-18 [38]	*Prevotellaceae*, TM7	[b]Exacerbated DSS colitis	
Alpha defensins [46]	SFB, *Bacteroides* (D)		
ACE2 [48]	*Limibacter*, *Paludibacter*	[b]Exacerbated DSS colitis	
Vitamin D receptor [53]	Desulfovibrionaceae, Bacteroidaceae, Erysipelotrichaceae	Exacerbated DSS colitis	
Cyp27B1 [53]	Desulfovibrionaceae, Bacteroidaceae, Erysipelotrichaceae	Exacerbated DSS colitis	
RegIIIγ [22]	SFB, *Eubacterium rectale*	Increased intestinal Th1 cells and IgA production	
RELMβ [68]	Bacteriodetes (A), Firmicutes (A), Proteobacteria (A)	Resistance to diet-induced obesity	
FUT2 [77–80]	Various (see text)		Crohn's disease, primary sclerosing cholangitis, psoriasis, type 1 diabetes
Innate lymphoid cells			
IL-22 [92,95]	SFB, *Alcaligenes* (I)		
[a]T-bet, with Rag [98,99]	*Klebsiella pneumonia, Proteus mirabilis, Helicobacter typhlonius*	[b]Spontaneous colitis	
Adaptive immunity			
μMT (i.e. no B cells in KO) [106]	*Paracoccus*, *Lactococcus*, Clostridiaceae (D)	Lipid malabsorption	
AID [107–109]	SFB, culturable anaerobes	Susceptibility to *Y. enterocolitica*	
iNOS and TNFα, B cells [110]	SFB (D)	Susceptibility to *C. rodentium*	
[a]PD1 [114]	Erysipelotrichaceae, Prevotellaceae, Alcaligenaceae, TM7	Arthritis, glomerulonephritis, cardiomyopathy	
CNS1 [116]	TM7, *Alistipes*	Enteritis, gastritis	
CD1d [122]	SFB, *E. coli*, *Pseudomonas aeruginosa*		
Other			
IRGM [135]	*Prevotella*		Crohn's disease
[a]Sialyltransferase [84]	Ruminococcaceae (D)	[b]Attenuated DSS colitis	
[a]Apolipoprotein A1 [85]	Rikenellaceae, Lachnospiraceae, Erysipelotrichaceae (D)	Impaired glucose tolerance, increased body fat	

[a] Denotes genes implicated in gardening by knockout mouse studies that did not use littermate controls from heterozygote breeding.
[b] Denotes phenotypes that can be attributed to the altered intestinal microbiota based upon co-housing experiments or reconstitution of germ-free mice. SFB = segmented filamentous bacteria.

stabilization into an adult microbiota distinct from (though still influenced by) the founding microbiota [15–17].

Since diet and founder effects, while important, do not alone explain taxonomic specificity of microbial composition, it is apparent that genetically encoded mechanisms exist to ensure that early fluctuations in intestinal microbiota result in the emergence of a stable, species-appropriate microbiota. Host factors that could potentially be utilized to regulate the microbiota include immune activity, intestinal motility, attachment surfaces, and secreted products that are metabolized by bacteria. The existence of host gardening of the intestinal microbiome has largely been probed by comparing the microbiota of mice deficient in a putative gardening gene to littermate controls using 16S ribosomal RNA sequencing. The vast majority of gardening genes identified in this manner are involved in innate (including epithelial) and adaptive mucosal immunity (Table 1).

2. Microbial sensing via pattern recognition receptors

The immune system is equipped with an intricate system of germline encoded pattern recognition receptors (PRRs) that recognize microbial molecular patterns. Many of the genes found to affect the microbiome are PRRs, suggesting that gardening is an active process in which mucosal cells adjust their gardening activity in response to microbial composition.

2.1. Toll-like receptors (TLRs)

TLRs are transmembrane PRRs that exist either on the cell surface – where they recognize external components of bacteria, mycoplasma, fungi, and viruses – or in the endolysosomal compartment, where they recognize microbial nucleic acids [18]. The cell surface TLRs include TLR1 (which recognizes lipoproteins),

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