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**Antibacterial weapons: targeted destruction in the microbiota**

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30 **Abstract**

31 The intestinal microbiota plays an important role in health, particularly in promoting intestinal  
32 metabolic capacity and in maturing the immune system. The intestinal microbiota also  
33 mediates colonization resistance against pathogenic bacteria, hence protecting the host from  
34 infections. On the other hand, some bacterial pathogens deliver toxins that target  
35 phylogenetically related or distinct bacterial species in order to outcompete and establish  
36 within the microbiota. The most widely distributed weapons include bacteriocins, as well as  
37 contact-dependent growth inhibition and type VI secretion systems. In this review, we discuss  
38 important advances about the impact of such antibacterial systems on shaping the intestinal  
39 microbiota.

## 40 **The intestinal microbiota: our best frenemy**

41           The mammalian intestine is inhabited by a large and diverse community of microbes,  
42 referred to as the gut microbiota. The human gut microbiota, also referred to as a "microbial  
43 organ", weights 1-2 kg, and consists of approximately 100 trillion ( $10^{14}$ ) bacteria representing  
44 6-10 phyla, including two predominant phyla – Bacteroidetes and Firmicutes –, and about  
45 500-1000 distinct species [1]. This highly complex **microbial community** (see Glossary) is  
46 controlled by various factors, such as host genetics and environmental factors. Moreover,  
47 microbiota diversity and composition is influenced by host diet as well as by positive and  
48 antagonistic interactions between bacteria within the microbiota.

49           The intestinal microbiota has an overall beneficial impact on its host, by providing  
50 metabolic activities within the intestine and favoring the development of the **intestinal**  
51 **immune system** [2] (**Figure 1**). Exemplifying this notion is the observation that the immune  
52 responses in mice housed in germ-free conditions are abnormal compared to conventionally-  
53 colonized mice [3, 4]. Therefore, early exposure to microbes in the intestine is a critical factor  
54 to modulate intestinal immune responses [5], and a well-documented example of a single  
55 microbial member playing a central role in shaping the intestinal immune system is  
56 segmented filamentous bacteria (SFB), which can promote the robust differentiation of Th17  
57 cells [6-8]. Moreover, if not well managed, the gut microbiota can become deleterious, for  
58 example by inducing uncontrolled intestinal inflammation. In light of the benefits the  
59 microbiota confers and on its potential to harm its host, the gut microbiota has previously  
60 been referred as the host's best frenemy [9].

61           Collectively, the microbiota and its derived metabolites are critical components for the  
62 maturation of host intestinal immunity, and research has accumulated on the central role  
63 played by the intestinal microbiota in the protection of the host intestine against pathogens, a  
64 phenomenon called colonization resistance [10-12]. Bacterial competition occurs either by  
65 depleting nutrients from the milieu (exploitation competition) or by deploying antibacterial

66 weapons to specifically eliminate target cells (interference competition) (**Figure 1**). Many  
67 bacteria can directly prevent intestinal pathogens colonization or overgrowth by consuming  
68 common limited resources, hence inducing starvation of competing pathogens. One example  
69 highlighting this mechanism of exploitation competition is the finding that the commensal  
70 *Bacteroides thetaiotaomicron* consumes carbohydrates used by the pathogen *Citrobacter*  
71 *rodentium*, thus leading to a competitive exclusion of the pathogen from the intestine [13, 14]  
72 (**Figure 1**). Through the production of specific metabolites, the intestinal microbiota can also  
73 modify the host environmental conditions, then compromising pathogen growth and/or  
74 virulence. Butyrate, a short-chain fatty acid (SCFA) produced by the intestinal microbiota,  
75 downregulates the expression of several virulence genes of *Salmonella enterica* serovar  
76 Enteritidis (*S. Enteritidis*) and Typhimurium (*S. Typhimurium*) [15] and inhibits the growth of  
77 enterohemorrhagic *Escherichia coli* (EHEC) [16] (**Figure 1**). Finally, members of the  
78 microbiota can affect the growth of other cells by producing and releasing inhibitory  
79 substances, such as antibiotics and peptide antibiotics, or by injecting antibacterial effectors  
80 into target cells. Here we will briefly describe the various mechanisms evolved by bacteria to  
81 destroy rivals and we will review recent studies on how these systems contribute to reshaping  
82 bacterial communities *in vivo*.

83

#### 84 **Bacterial weapons in the intestine**

85 To combat competitors, bacteria deploy a broad arsenal of antibacterial weapons.  
86 These weapons vary in terms of mechanism of action, toxin targets, and mode of penetration,  
87 and hence limit the acquisition of mechanism of resistance by competitors. The most widely  
88 distributed weapons in Enterobacteria are microcins and bacteriocins [17], contact-dependent  
89 growth inhibition (CDI) [18] and Type VI secretion systems (T6SS) [19] (**Figure 2**). Other  
90 mechanisms, such as Type I, Type IV and Type VII secretion systems or outer membrane

91 exchange, have also been recently shown to mediate toxin delivery into competitors or to  
92 promote contact-dependent killing [20-25].

93 Bacteriocins are a group containing a large variety of proteinaceous antibiotics of  
94 various lengths: microcins are 15-60 amino-acid peptides, lantibiotics are peptide containing a  
95 modified amino-acid (lanthionine), whereas colicin-like proteins are > 40 kDa multidomain  
96 proteins and tailocins are high molecular weight multiprotein complexes resembling  
97 bacteriophage tails [26-29]. Bacteriocins are produced upon stress conditions, and share a  
98 similar mechanism of action. After release, they bind to an outer membrane receptor and  
99 parasitize cell envelope components for penetration [26, 27, 30] (**Figure 2**). The exploitation  
100 of specific reception and translocation machineries restrict the action of these toxins to the  
101 same or phylogenetically related species. Cell toxicity is conferred by pore-forming activity  
102 that collapses the membrane potential at the inner membrane, by digestion or cleavage of  
103 nucleic acids or of cell wall precursors [26, 30]. Bacteriocins include S-type pyocins liberated  
104 by *Pseudomonas* species, and colicins that are produced by enteric strains such as *E. coli*, *C.*  
105 *rodentium* and *Enterobacter* species [26, 30].

106 By contrast to bacteriocins that are diffusible toxins, CDI and T6SSs are cell-cell  
107 contact-dependent mechanisms. CDI is a variant of two-partner secretion, a family of Type V  
108 secretion systems widely represented in Proteobacteria [31-33]. It comprises two proteins: the  
109 CdiB outer membrane transporter translocates the CdiA protein to the cell surface. CdiA are  
110 usually elongated spring-like  $\beta$ -helical structures that carry a C-terminal toxin domain. The C-  
111 terminal domain mediates target cell recognition, penetration and toxicity (**Figure 2**). Similar  
112 to bacteriocins, the requirements for specific receptors and target cell factors restrict the  
113 action of CDI to close relatives [18, 31, 34, 35].

114 T6SS is a more complex machinery, broadly distributed in Proteobacteria and  
115 Bacteroidetes. Its assembly requires at least 13 components to form a speargun-like weapon  
116 [19, 36, 37]. T6SS could be considered as a bacteriophage-like contractile tail structure

117 anchored to the cell envelope [19, 38, 39]. The tail is constituted of an effector-loaded syringe  
118 wrapped by the sheath that is built under a metastable, extended conformation [19, 36, 37, 40-  
119 42]. Contraction of the sheath presumably propels the syringe towards the rival cell, and thus  
120 delivers effectors to cause cell damages [40, 42-46] (**Figure 2**). How the target cell is sensed  
121 and how cell-cell contact triggers T6SS assembly or firing is largely unknown but in certain  
122 cases, transcriptional, post-transcriptional or post-translational regulatory cascades, cell-  
123 envelope damage or the presence of kin cell components in the milieu trigger a T6SS  
124 response to attacks [44, 46-52]. By contrast to bacteriocins and CDI, T6SSs do not exploit  
125 specific receptors, and hence target a broader range of bacteria, although no T6SS-dependent  
126 damages of Gram-positive bacteria have been observed [53]. T6SS antibacterial effectors  
127 include peptidoglycan-acting enzymes (amidases, glycosyl hydrolases), membrane-targeting  
128 proteins (phospholipases and pore-forming), nucleases and NAD(P)(+) glycohydrolases [53-  
129 59]. Interestingly, the T6SS is also capable of delivering effectors into eukaryotic cells,  
130 including single-celled microorganisms and animal tissues [54, 60]. Phospholipases and  
131 nucleases can act as trans-kingdom effectors, but specialized toxins, such as those interfering  
132 with cytoskeleton or tubule dynamics, have been identified and characterized [60-67].

133 For all these systems, attacker bacteria are protected from self-intoxication and  
134 intoxication by kin cells by the production of immunity proteins that usually bind with high  
135 affinity and inhibit the catalytic activity of the cognate effector [26, 31, 34, 54, 55, 68, 69].

136 In addition, some enteric pathogens can produce broadly bioactive small molecules  
137 such as antibiotics, non-ribosomal peptide antibiotics, sactibiotics and lantibiotics [70-72],  
138 that may act toward other members of the intestinal microbiota and/or toward enteric  
139 pathogens. Finally, other extracellular contractile injection systems such as R-pyocins, anti-  
140 feeding prophages (Afp) and Afp-like particles have antibacterial or antimicrobial activities  
141 [73-75].

142           Although the role of these systems in antibacterial competition is well documented *in*  
143 *vitro*, studies have only begun to investigate their contribution in *in vivo* animal models.

144

### 145 **Role of bacterial competition in the intestinal microbiota**

146           The gut microbiota is a very stable ecosystem [1]. However, the invasion or  
147 overgrowth of pathogens induces **dysbiosis**, an instability that may alter the composition of  
148 the microbiota but also host physiology [11, 76-78]. It is now well appreciated that  
149 interference competition between members of the microbiota, in addition to indirect  
150 competition such as exploitation competition, plays a central role in microbiota ecology [78].

151           Until recently, the role of interbacterial competition in shaping bacterial communities  
152 has been underestimated [79]. However, antibacterial weapons are key players in the control  
153 of bacterial populations, and a summary of known examples of *in vivo* bacterial competition  
154 is presented in **Table 1**. The importance of these weapons *in vivo* is supported by the  
155 estimation that more than  $10^9$  T6SS firing events occur per minute per gram of colonic  
156 contents [80]. T6SS gene clusters are highly represented in Bacteroidales strains, which  
157 account for a large portion of the gut microbiota [81, 82]. In addition, many Gram-negative  
158 enteric pathogens, including *Vibrio cholerae*, *S. Typhimurium*, *C. rodentium*, and *Shigella*  
159 *sonnei* utilize functional T6SSs to fire against other species *in vitro* [83, 84]. In agreement  
160 with the concept that T6SSs are important players in bacterial competition within the  
161 intestine, a number of enterobacterial T6SS gene clusters are upregulated in conditions  
162 encountered in the gut or when a threshold of cell density is reached [85]. The *V.*  
163 *cholerae* T6SS is activated by mucins and microbiota-modified bile salt [86]; the *S.*  
164 *Typhimurium* T6SS is activated by bile salts [87]; and the enteroaggregative *E. coli* Sci-1  
165 T6SS is responsive to iron starvation [88].

166           *V. cholerae*, *S. Typhimurium* and *S. sonnei* deploy their T6SSs to kill or displace  
167 commensal bacteria, allowing a successful colonization of the host and an increased



168 persistence in experimental models [89-92]. Using transposon insertion site sequencing (Tn-  
169 Seq) to identify *V. cholerae* mutants that exhibit a colonization defect in the rabbit intestine,  
170 Fu *et al.* found *tsiV3*, encoding immunity to the T6SS VgrG3 peptidoglycan hydrolase  
171 effector [93]. Interestingly, a recent study demonstrated that *V. cholerae* T6SS-mediated  
172 colonization specifically occurs in intestinal microenvironments, such as the middle small  
173 intestine, suggesting that T6SS effectors might target specific species [94]. The antagonistic  
174 behavior of *V. cholerae* in the gut triggers intestinal colonization, virulence gene expression,  
175 and host innate immune response [95]. In a recent study, Sana and collaborators demonstrated  
176 that the successful establishment of *S. Typhimurium* in the mouse intestine requires the T6SS  
177 Tae4 amidase effector [87]. Thus, the observation that bacterial-specific effectors are required  
178 for efficient colonization demonstrates that the T6SS mediates antagonistic interbacterial  
179 interactions during infection. It is not yet known whether T6SS specifically targets certain  
180 species, but the observation that *S. Typhimurium* targets *Klebsiella oxytoca* and has only  
181 weak impact on other species suggests that the T6SS does not fire randomly [87].  
182 Interestingly, *S. Typhimurium* and *K. oxytoca* utilize the same carbon sources and thus the  
183 specific elimination of a metabolic competitor may provide a better access to the available  
184 nutritional resources [79]. Another example of T6SS-mediated metabolic competition is the  
185 secretion of manganese- and zinc-scavenging enzymes by pathogens such as *Burkholderia*  
186 *thailandensis* [96, 97]. In addition, EHEC uses its T6SS to secrete catalases, thus providing a  
187 higher resistance to reactive oxygen species produced by the host [98]. A recent example of  
188 the importance of the T6SS in intestinal colonization is related to the increased prevalence of  
189 *S. sonnei* infections over that of the close relative *Shigella flexneri*. By contrast to *S. flexneri*,  
190 the genome of *S. sonnei* encodes a functional T6SS that confers a competitive advantage by  
191 outcompeting *S. flexneri in vitro* as well as in the mouse gut [90]. Interestingly, *S. sonnei* also  
192 encodes the ColE1 colicin that enables *E. coli* elimination [90]. Those recent findings are in  
193 agreement with the observation that colicinogenic *E. coli* cells present an increased intestinal

194 persistence compared to the isogenic *E. coli* strain unable to produce colicins [99, 100]. Other  
195 bacteriocins and R-pyocins have the ability to destroy rivals in biofilm or mixed communities,  
196 and to specifically eliminate bacterial species after therapeutic administration; and hence are  
197 proposed to be viable alternatives to antibiotics [101-105].

198         While the above examples showed that antibacterial weapons are used by pathogens to  
199 colonize their hosts, the gut microbiota also exerts an important control to prevent  
200 colonization by pathogens [106, 107]. Indeed, many commensal strains produce those  
201 weapons and therefore protect the niche against the invasion of external microbes or against  
202 the overgrowth of indigenous pathogens. An elegant example is the recent observation that  
203 the probiotic strain *E. coli* Nissle uses microcins M and H47 to limit the expansion of  
204 competing Enterobacteriaceae, including pathogens such as adherent-invasive *E. coli* (AIEC)  
205 and *S. Typhimurium* during intestinal inflammation [108]. Another example is *Bacillus*  
206 *thuringiensis*, a bacterium able to secrete a bacteriocin (thuricin CD) that directly targets  
207 spore-forming Bacilli and Clostridia, including *Clostridium difficile* [109].

208         Other commensals, such as those of the Bacteroidales order, antagonize gut microbiota  
209 using secreted antimicrobial proteins or T6SS [56, 110-113]. Interestingly, it has been shown  
210 that intense transfer of genetic material occurs between Bacteroidales species in the gut [82].  
211 As a consequence, Bacteroidales have accumulated genes encoding immunity proteins to  
212 T6SS effectors they do not encode [80], and thus maintain a stable balance in the microbiota  
213 by preventing their own elimination. In addition, the symbiotic *Bacteroides fragilis* strain was  
214 shown to use the T6SS to harm enterotoxigenic *B. fragilis* cells, demonstrating that the  
215 activity of Bacteroidales T6SSs may protect the host against intestinal inflammatory diseases  
216 [114]. Altogether, these data demonstrate that a broad range of competitive mechanisms  
217 occurs within the intestinal microbiota and plays a role in microbiota composition,  
218 establishment, stability, and evolution.

219

## 220 **Concluding Remarks**

221 Future studies will be needed to further characterize mechanisms by which bacteria  
222 compete within the intestinal tract, with a particular focus on long-lasting consequences on  
223 microbiota composition and host physiology (see Outstanding Questions). Long-term  
224 experiments are also required to understand the real contribution of antibacterial weapons in  
225 shaping microbial communities. At present, it is not clear whether being well armed  
226 represents a true advantage, as antibacterial weapons have limited impact on well-structured  
227 communities [115]. In addition, microbial communities are subjected to a rock-paper-scissor  
228 game, in which the production of these weapons is energetically consuming, and hence  
229 attacker cells might be defeated by professional cheaters or by strains with a better fitness  
230 [116, 117].

231 Another important field of research that needs further investigation is the impact that  
232 such antimicrobial systems may have on both microbiota composition and host physiology in  
233 the long term. An example highlighting the importance of interbacterial competition in long  
234 term dysbiosis is the observation that intestinal colonization of AIEC, an *E. coli* pathovar  
235 associated with Crohn's disease, causes alteration of microbiota composition and chronic  
236 colitis in mice, with both phenotypes persisting well beyond AIEC clearance [118]. Hence, in  
237 addition to their own virulence potential, AIEC bacteria are able to induce chronic  
238 inflammation by detrimentally altering the intestinal microbiota composition [118]. While the  
239 precise role played by antibacterial systems in such long-term alterations still needs to be  
240 investigated, they may further highlight the unappreciated importance of such  
241 bacteria/bacterial competition in microbiota stability and host physiology.

242 Finally, such antibacterial mechanisms may be tailored in a near future as an  
243 alternative or complementary approach to the use of antibiotics. A few bacteriocins, such as  
244 nisin, have been validated by the FDA and are used as food preservatives [119]. While such  
245 compounds are used to extend shelf life, we still ignore their impact on the intestinal

246 microbiota. In addition, colicins, R-pyocins, CdiA and T6SS effectors are modular proteins  
247 and hence might be genetically engineered to specifically target bacterial populations of  
248 interest. Modified colicins, R-pyocins or T6SS effectors have already been demonstrated to  
249 be efficiently delivered into target cells or to destroy specific species without affecting the gut  
250 microbiota diversity [87, 95, 120-124]. One may predict that these initial attempts will be  
251 actively pursued to deliver toxins or CRISPR/Cas system into specific species, with the  
252 ultimate goal to prevent intestinal colonization or to beneficially reshape an altered microbial  
253 ecosystem.

254

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533

534 **Glossary**

535 **Dysbiosis:** microbial population with an imbalanced composition, often associated with  
536 deleterious impact for the host. Dysbiosis has been identified as an important player of  
537 inflammation in inflammatory bowel diseases.

538 **Intestinal immune system:** The complex population of cells and interactions inhabiting our  
539 intestine with the dual role of tolerance toward our commensal microbiota and protection  
540 against intestinal pathogen. Importantly, the intestine represents the largest compartment of  
541 the immune system, with the estimation that 70% of the mammalian immune system is hosted  
542 within the intestine.

543 **Microbial community:** mixed population of bacteria and single-cell microorganisms.  
544 Microbial communities include microbiota, but also biofilms (bacteria that adhere to a  
545 support) and consortiums (bacteria that exchange metabolic contents).

546

547 **Legend to Figures**

548 **Figure 1. Commensal microbiota-mediated colonization resistance in the intestine.** The  
549 intestinal microbiota plays a central role in both intestinal barrier maintenance and immune  
550 system maturation. Examples of microbiota-mediated inhibition of intestinal colonization by  
551 enteric pathogens are represented: exploitation competition (utilization of nutrient resources),  
552 and interference competition (production of virulence gene repressor molecules or  
553 antibacterial weapons). EHEC, enterohaemorrhagic *Escherichia coli*.

554

555 **Figure 2. The arsenal of antibacterial weapons.** The major antibacterial weapons used by  
556 enteric bacteria and their mechanism of action are schematically represented. Bacteriocins  
557 (green) are diffusible multi-domain proteins that are produced and released by the attacker  
558 cell. The reception (R) domain binds to the specific receptor and the translocation (T) domain  
559 helps the translocation of the activity (A) domain into the target. Contact-dependent growth  
560 inhibition (CDI, orange) comprises the CdiB translocator and CdiA toxin. The CdiA C-  
561 terminal domain (Ct) binds to a specific receptor and translocates to the target cell. Type VI  
562 secretion system (T6SS, blue) is an injection system that uses a contractile mechanism to  
563 propel an effector-loaded needle into the target.

564

565 **Table 1. Summary of known *in vivo* bacterial competition.**

Bacterium	Weapon	Target cell	Toxin / Activity	Reference
<i>Salmonella enterica</i> Typhimurium	T6SS	<i>Klebsiella oxytoca</i>	Tae4 (amidase)	[87]
<i>Bacillus thuringiensis</i>	Bacteriocin thuricin CD	Spore-forming Bacilli and Clostridia, including <i>C. difficile</i>	pore-forming	[109]
<i>Burkholderia thailandensis</i>	T6SS	unknown	unknown	[96, 97]
EHEC	T6SS	-	Catalases	[98]
<i>Shigella sonnei</i>	T6SS	<i>S. flexneri</i>	Unknown	[90]
<i>Shigella sonnei</i>	ColE1 colicin	<i>E. coli</i>	Pore-forming	[90]
<i>E. coli</i> Nissle	Microcins M and H47	Enterobacteriaceae, including pathogens such as AIEC and <i>S. Typhimurium</i>	unknown	[108]
<i>Bacteroides fragilis</i>	T6SS	<i>B. fragilis</i> , gut microbiota and pathogenic bacteria	Bte2	[56, 110, 114]
<i>V. cholerae</i>	T6SS	commensal <i>E. coli</i>	unknown	[95]

566

567

## **Outstanding Questions Box**

- How do antibiotics and antibacterial molecules alter the intestinal microbiota composition and affect colonization resistance?
- What are the direct impacts of antibacterial weapons in the gut?
- What is the contribution of the antibacterial weapons of commensals in the protection of the host against pathogens?
- What is the target range of T6SS and what is the cost to produce antibacterial weapons?
- Is it a real benefit for the bacterium to be equipped with antibacterial weapons?
- How can antibacterial weapons be genetically modified for therapeutic purposes in order to manipulate the intestinal microbiota in beneficial ways?
- What are the long term impacts of such antibacterial systems on the microbiota community and host physiology?

## **Trends Box**

- The intestinal microbiota is a complex but stable ecosystem that plays a central role in human health, and disturbance of its composition and function is associated with many diseases.
- Within the intestinal microbiota, bacteria exchange material and information.
- The microbiota can be peaceful, but many bacteria fight with others to have a better access to their niche or nutrients.
- Different antibacterial weapons have been identified and characterized, and many bacterial pathogens use these weapons to establish themselves in the intestinal environment, whereas some commensals use these weapons to specifically target pathogens, leading to protection of the host.





