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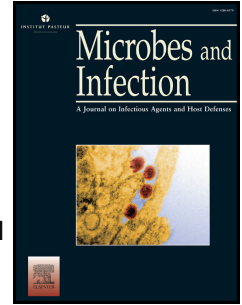
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**Control of pathogens and microbiota by innate lymphoid cells**

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15 **Summary**

16 Innate lymphoid cells (ILCs) are the innate counterpart of T cells. Upon infection or injury,  
17 ILCs react promptly to direct the developing immune response to the one most adapted to the  
18 threat facing the organism. Therefore, ILCs play an important role early in resistance to  
19 infection, but also to maintain homeostasis with the symbiotic microbiota following  
20 perturbations induced by diet and pathogens. Such roles of ILCs have been best characterized  
21 in the intestine and lung, mucosal sites that are exposed to the environment and are therefore  
22 colonized with diverse but specific types of microbes. Understanding the dialogue between  
23 pathogens, microbiota and ILCs may lead to new strategies to re-inforce immunity for  
24 prevention, vaccination and therapy.

25

26 **Keywords:** Innate lymphoid cells, microbiota, pathogens, homeostasis, mucosal immunity

27

28

## 29 I. Introduction

30 ILCs derive from a lymphoid cell precursor common with T cells, with whom they share  
31 phenotypes and functions [1,2]. However, T cells are antigen-specific, carry immunological  
32 memory, and are selected by their cognate antigen in lymph nodes and Peyer's patches before  
33 expansion. Once activated, T cells recirculate through the blood to reach organs where their  
34 effector functions are required, eventually committing apoptosis or remaining in tissues as  
35 resident memory T ( $T_{RM}$ ) cells [3]. Nevertheless, the process of T cell selection, activation  
36 and recirculation requires several days, leaving the early phase of the immune response  
37 without T cell-mediated orchestration of the response best adapted to the type of threat faced  
38 by the individual. However, early orchestration is directed by ILCs, which perform similar  
39 regulatory functions and provide prompt effector responses to infection and injury. ILCs also  
40 play important roles early in life, when the adaptive immune system is not yet in place [1].

41 An individual faced with intracellular threats, such as tumors, viruses and particular  
42 bacteria, responds with type 1 immune responses characterized by the production of type I  
43 interferons, the inducer cytokine IL-12, the effector cytokine  $IFN\gamma$ , the release of cytotoxic  
44 oxygen radicals and proteins, and the elimination of the transformed or infected cells (Figure  
45 1). Extracellular microbes, such as bacteria and fungi, elicit type 3 responses that are  
46 characterized by the release of the inducer cytokine IL-23 and the production of the effector  
47 cytokines IL-17 and IL-22, which lead to the reinforcement of mucosal barriers and the  
48 recruitment of polymorphonuclear neutrophilic phagocytes that target, ingest and destroy the  
49 microbes. In contrast, when faced with large parasites, such as worms, the individual develops  
50 type 2 responses that lead to the release of fluids and the production of mucus at mucosal  
51 surfaces, and the deposition of collagen to resist parasite penetration. The type 2 inducer  
52 cytokines are IL-25, IL-33 and TSLP, which lead to the production of the effector cytokines  
53 IL-4, IL-5 and IL-13. Myeloid cells and stromal cells produce the appropriate inducer  
54 cytokines in response to a specific type of threat, activating ILCs and T cells to differentiate  
55 into ILC1s and Th1, ILC2s and Th2, or ILC3s and Th17, which produce the effector  
56 cytokines characteristic of type 1, 2 and 3 immunity [1,4].

57 Importantly, these immune responses are not only engaged in response to pathogens  
58 and tissue injury, but also in response to the symbiotic microbiota [5]. Microbes are present at  
59 all mucosal surfaces, as well as within tissues. An estimated  $10^{14}$  bacteria reside in the  
60 intestine, together with viruses, fungi, protists and occasional worms, while smaller yet  
61 significant collections of microbes are present in the oral cavity, genitourinary system and  
62 skin [6,7]. Furthermore, the list of viruses found within our organism is expanding [8], and

63 bacteria have been identified in lymphoid tissues [9,10] and placenta [11]. As a consequence,  
64 the immune system is constantly activated by the presence of these diverse symbiotic  
65 microbes. We have therefore argued that the primary function of the immune system is to  
66 maintain homeostasis of the host with its microbiota [5], a microbiota that is necessary for  
67 digestion, production of metabolites and defense. In contrast, if microbes are associated with  
68 injury of the host's cells and tissues, the immune reaction will lead to the elimination of the  
69 pathogens.

70 In this review, we discuss the role of ILCs in the control of the symbiotic or  
71 pathogenic microbiota (Figure 2 and Table 1). From recent data, it emerges that ILCs play  
72 unique roles in microbiota control, observations that may lead to a new understanding of how  
73 chronic inflammatory pathologies emerge when such control is lost, and create new  
74 opportunities for prevention and therapy of infectious diseases. We will not discuss the role of  
75 NK cells, the oldest member of the ILC family, which has been extensively studied since 40  
76 years and best reviewed elsewhere [12].

77

## 78 **II. ILCs in the control of intestinal and hepatic infections**

79 ILC3s are the oldest and best characterized ILC family member (not considering NK cells). In  
80 the late 90's, non-B non-T lymphoid cells, termed lymphoid tissue inducer (LTi) cells, have  
81 been described that colonize developing secondary lymphoid tissues, the lymph nodes and the  
82 Peyer's patches, and shown to be required for their development [13,14]. LTi cells form  
83 clusters in fetal lymphoid tissues and the intestinal lamina propria [15], and activate stromal  
84 cells to initiate organogenesis [16]. Ten years later, it was shown that LTi cells are part of a  
85 larger family of ILC3s that depend on the hormone receptor and transcription factor ROR $\gamma$ t  
86 [17], and express the type 3 cytokines IL-17, IL-22 and lymphotoxin (LT) [18-21]. Non-LTi  
87 ILC3s do not cluster and are not involved in the development of lymphoid tissues. Rather,  
88 these cells resemble more freely moving lymphoid effector cells, and together with LTi cells,  
89 play a critical role early in defense against enteric pathogens.

90 Using mouse models that lack all lymphoid cells or only B and T cells, it was reported  
91 that ILC3s are required early in the control of intestinal infection by *Proteobacteria*, such as  
92 *Citrobacter rodentium*, the murine homologue of human enteropathogenic *Escherichia coli*.  
93 The production of IL-22 is paramount for this protective function, and induces the expression  
94 of anti-microbial peptides (AMPs) by epithelial cells, such as Reg3 $\gamma$  [18,21-23]. Also  
95 involved in increasing epithelial defense is membrane-bound LT, which bind its receptor

96 LT $\beta$ R on epithelial cells and induces expression of the neutrophils chemoattractants CXCL1  
97 and CXCL2 [24]. Furthermore, ILC3s are involved in the response to infection by *Salmonella*  
98 *enterica* through the production of IL-17 and IL22, as well as IFN $\gamma$  [25]. The production of  
99 IL-17 by ILC3s and the recruitment of neutrophils are essential in the response to infection by  
100 *E.coli K1* and *Klebsiella pneumoniae* and to prevent sepsis [26]. The protective role of ILC3s  
101 against pathogens extends to parasites and viruses. Infection by *Toxoplasma gondii* leads to  
102 more severe inflammatory pathology in the absence of ILC3s, presumably because of a failure  
103 to contain the parasites early [27]. Furthermore, IL-22 production by ILC3s potentiates the  
104 activity of IFN $\lambda$  in epithelial cells and thus increases resistance to rotavirus [28]. However,  
105 the pro-inflammatory activity of ILC3s may also lead to pathology through the production of  
106 IFN $\gamma$  in the context of *S. enterica* infection [25], as well as intestinal fibrosis through the  
107 expression of IL-17 and IL-22 in the context of *S. typhimurium* infection [29].

108 ILC2s were first reported in the context of intestinal infection with the helminth  
109 *Nippostrongylus brasiliensis*, which evokes a vigorous expansion of “non-B non-T cells”  
110 expressing IL-4, IL-5 and IL-13 [30,31]. ILC2s are also involved in defense against  
111 *Heligmosomoides polygyrus* [32], *Strongyloides venezuelensis* [33], *Trichinella spiralis* [34]  
112 and *T. muris* [35], and are diminished in the blood of children infected with the blood dweller  
113 *Schistosoma haematobium* [36]. Both inducer cytokines IL-25 and IL-33 are expressed upon  
114 helminth infection and activate ILC2s, noting that ILC2s responding to IL-33 have been  
115 suggested to be precursors of ILC2s responding to IL-25 [37]. While IL-33 is expressed by  
116 different types of stromal cells, as well as by mast cells [32], the source of IL-25 was only  
117 recently identified, in the intestine, as Tuft epithelial cells [38-40]. Interestingly, Tuft cells  
118 appear to detect helminth infection through chemosensory signaling via the G-protein coupled  
119 receptor Trpm5 [38]. The activity of ILC2s is also promoted, during helminth infection, by  
120 the neuropeptide neuromedin U that is expressed by cholinergic neurons in the intestine  
121 [41,42].

122 ILC1s are distinguished from NK cells by their lack of expression of, and requirement  
123 for, the transcription factor Eomesodermin [2]. ILC1s provide early protection to the liver  
124 from mouse cytomegalovirus infection, producing IFN $\gamma$  before NK cells are engaged [43], but  
125 at the same time prevent the recruitment of NK cells and CD8<sup>+</sup> T cells that optimally fight  
126 liver infection with adenovirus [44]. Mouse hepatitis virus inoculated orally is also cleared  
127 from the intestine by ILC1s, which are activated by IL-15 released from infected stromal cells  
128 [45]. Furthermore, ILC1s and their production of IFN $\gamma$  are engaged in the defense against

129 bacteria, such as *Clostridium difficile* [46]. Nevertheless, ILC1s and NK cells have largely  
130 overlapping function, even though ILC1s are defined as non-cytotoxic. As both cells types  
131 react promptly to activators such as IL-12, their relative role is mostly dependent on their  
132 tissue distribution before infection.

133

### 134 **III. The ILC crosstalk with intestinal microbiota**

135 The large intestinal microbiota has been best characterized, so far, at the level of its  
136 bacteriome and of its cross-talk between symbiotic bacteria and ILC3s. In contrast, the  
137 interaction between the virome and ILCs remains largely unexplored, and ILC2s are not  
138 known to cross-talk with microbes, even though some bacteria have been reported to induce  
139 the expansion of ILC2s at the steady state [47]. Therefore, this chapter will discuss mostly our  
140 knowledge on the cross-talk between bacterial symbionts and ILC3s.

141 In 2008, we reported that peptidoglycan released by proliferating Gram<sup>-</sup> bacteria in the  
142 intestine induce the activation of LT<sub>i</sub> cells clustered in so-called cryptopatches [15], which are  
143 found near the base of crypts in the small intestine [48]. LT<sub>i</sub> cells in turn activate underlying  
144 stromal cells to release chemokines and recruit CCR6<sup>+</sup> B cells to form isolated lymphoid  
145 follicles (ILFs). ILFs generate microbiota-specific IgA-producing B cells, in a T-cell  
146 independent way, and play an important role in intestinal homeostasis [15,49]. The colonizing  
147 microbiota is therefore involved in the development of the intestinal immune system. At the  
148 same time, it provides a negative feedback on the number and activity of ILC3s, which  
149 include LT<sub>i</sub> cells, by inducing epithelial cells to produce IL-25 [47]. Of note, in both these  
150 phenomena, epithelial cells translate the recognition of microbes into signals that regulate  
151 ILCs.

152 Myeloid cells are nevertheless the major relay between microbiota and ILC3s through  
153 the production of the type 3 inducer cytokines IL-23 and IL-1 $\beta$ . In the context of *C.*  
154 *rodentium* infection, CX<sub>3</sub>CR1<sup>+</sup> macrophages produce higher amounts of these cytokines than  
155 do conventional CD103<sup>+</sup> DCs, and thus, more efficiently induce the expression by ILC3s of  
156 IL-22 [50] and GM-CSF [51]. In addition, CD11b<sup>+</sup> DCs, which include CX<sub>3</sub>CR1<sup>+</sup> cells, are  
157 obligate sources of IL-23 for host survival during *C. rodentium* infection [52], and TNF $\alpha$   
158 produced by CD11b<sup>+</sup> DCs during *Helicobacter typhlonius* infection synergizes with IL-23 for  
159 the expression of IL-17 by ILC3s [53]. CD11b<sup>+</sup> DCs are also activated by microbiota-derived  
160 ATP to produce IL-23 during the steady state [54]. Other members of the symbiotic  
161 microbiota induce the expression of IL-23 by myeloid cells and as a consequence, IL-22 by  
162 ILC3s, such as SFB [55] and *Lactobacilli* species [56]. ILC3s feedback positively on the



163 production of IL-23 by myeloid cells through their expression of membrane-bound LT and  
164 activation of LT $\beta$ R on DCs [57]. Unexpectedly, intestinal glial cells sense microbiota through  
165 a Myd88-dependent pathway and produce neurotrophic factors that activate the Ret receptor  
166 on ILC3s and promote their expression of IL-22 [58].

167 At the steady state, ILC3s are the major source of IL-22 [47]. IL-22, as well as IL-17,  
168 induce the production of AMPs by epithelial cells [59], and therefore, are critical for the  
169 containment not only of pathogens, but also of the symbiotic microbiota. IL-22 also regulates  
170 the fucosylation of epithelial cells, a dietary carbohydrate for many symbionts, and thereby  
171 increases resistance to infection by *Salmonella typhimurium* [60] and *C. rodentium* [61].  
172 Furthermore, membrane-bound (LT $\alpha_1\beta_2$ ) and soluble (LT $\alpha_3$ ) LT expressed by ILC3s play an  
173 important role in the containment of the microbiota [62] through the activation of epithelial  
174 cells [24], as well as of DCs and T cells that lead to the production of anti-microbial IgA [63].  
175 The containment of microbiota through the enhancement of epithelial defenses and adaptive  
176 immunity must nevertheless be controlled to avoid exaggerate responses to the symbiotic  
177 microbiota and consequent pathologic inflammation. To this end, ILCs express MHC class II  
178 molecules, as well as the machinery required to process proteins for presentation of peptides  
179 onto class II molecules, allowing ILCs to dampen the CD4<sup>+</sup> T cell response to microbiota [64]  
180 and to SFB in particular [65]. Reciprocally, the presence of CD4<sup>+</sup> T cells in the intestinal  
181 lamina propria decreases the expression of IL-22 by ILC3s [47,66], presumably through  
182 competition for survival and inducing cytokines such as IL-23.

183 Bacterial symbionts of the *Alcaligenes* genus have been identified that are present in  
184 Peyer's patches. ILC3s and IL-22 are critical for the containment of *Alcaligenes*, as the  
185 depletion of ILCs using an anti-CD90 antibody leads to the presence of the bacteria in spleen  
186 and liver [9]. The depletion experiments were performed in Rag-deficient mice, as well as in  
187 mice reconstituted with mature B and T cells, indicating that adaptive immunity is not  
188 necessary for the containment of *Alcaligenes*. It remains nevertheless possible that, in normal  
189 mice, adaptive immunity develops over time that contributes to the containment of these  
190 symbionts through the generation of antibodies. As a matter of fact, *Alcaligenes* promotes the  
191 generation of IgA, which contribute to the construction of its niche [10].

192

#### 193 **IV. Microbe-ILC interactions in the lungs**

194 The impact of ILCs on microbes (and parasites) at mucosal sites other than the intestine has  
195 been best studied in the lungs. ILC2s are the dominant ILC subset in the lungs at the steady  
196 state, as a consequence of the production of IL-33 and TSLP by the alveolar epithelium [67].

197 The production of IL-5 and IL-13 by ILC2s promotes the recruitment of eosinophils, the  
198 differentiation of monocyte into M2 (or alternatively activated) macrophages, and the  
199 differentiation of T cells into Th2 cells [68-70]. ILC2s contribute to the resistance to lung  
200 parasites, such as *Strongyloides venezuelensis* [71], *Nippostrongylus brasiliensis* [72,73],  
201 *Litomosoides sigmodontis* [74], as well as to tissue repair [75]. However, type 2 immunity  
202 induced by ILC2s also leads to increased susceptibility to fungal [76,77] and bacterial  
203 infection [78], by mechanisms of immunological cross-regulation [4].

204 Type 2 immunity promoted by ILC2s plays an important role in the repair phase of  
205 immune responses, which occurs, for example, after influenza A virus infection through the  
206 production of the EGFR ligand amphiregulin [79]. This repair response is nevertheless  
207 inhibited by IFN $\gamma$  that is induced by the virus infection [80]. Furthermore, the ILC2-initiated  
208 repair responses, induced by virus-induced tissue damage, can lead to exacerbated type 2  
209 responses and, as a consequence, asthma. Such an association, and the mechanisms driving  
210 this association, have been reported in the context of infection with rhinovirus [81-83] and  
211 respiratory syncytial virus [84,85]. Similar pathological consequences are also induced by the  
212 fungi *Alternaria alternata* [86] and *Cryptococcus neoformans* [87].

213 ILC3s also play an important role in the lungs in response to bacterial and fungal  
214 infections. IL-22 produced by ILC3s is instrumental in lung immunity to *Streptococcus*  
215 *pneumoniae* [88] and *Pseudomonas aeruginosa* [89]. Interestingly, neonatal colonization of  
216 mice with intestinal bacteria induces the influx of IL-22-producing ILC3s into the lung, which  
217 confer life-saving resistance to early infection by *Streptococcus pneumoniae* [90].

## 218

### 219 **V. Concluding remarks**

220 We have discussed recent data showing the critical role played by ILC early in the immune  
221 responses to pathogens, as these cells can respond promptly to inducer cytokines provided by  
222 myeloid and epithelial cells upon infection and injury. Of note, T<sub>RM</sub> cells, as well as particular  
223 subsets of invariant T $\alpha\beta$  or T $\gamma\delta$  cells, can play similar roles as their activation state alleviates  
224 the requirement for antigen-specific TCR activation. The prompt activation of ILCs is also  
225 important in response to changes in the symbiotic microbiota, in order to maintain  
226 homeostasis.

227 The current knowledge on the role of ILCs in defense and homeostasis has been  
228 inferred from mouse models and association studies in human. It is now possible to design  
229 strategies to harness the central role of ILCs in homeostasis, defense and immunoregulation  
230 for the prevention and therapy of infectious diseases, and of pathological consequences of

231 microbiota dysbiosis. It is also possible that novel vaccination strategies benefit from an early  
232 manipulation of ILCs, in order to force the response to specific antigens into the type most  
233 adapted to fight the pathogen. The manipulation of ILCs may involve the administration of  
234 inducer cytokines, or other molecules, yet to be discovered, that specifically activate subsets  
235 of ILCs. Another possibility is the isolation of ILC precursors from the blood of patients, and  
236 their expansion *in vitro* into the desired subset before re-administration and induction of type  
237 1, 2 or 3 immune responses. We are still in the early days of ILC biology, but also at the  
238 exciting transition phase when clinical applications become possible.

239

240 **Table 1**

ILC type	Role	Microbe type	Microbe species	Organ	References
ILC1	+	Bacteria	<i>Clostridium difficile</i>	Intestine	[46]
	+	Virus	<i>Adenovirus</i>	Liver	[44]
	+		<i>Mouse hepatitis virus</i>	Liver	[45]
	+		<i>Cytomegalovirus</i>	Liver	[43]
ILC2	-	Bacteria	<i>Streptococcus pneumoniae</i>	Lung	[78]
	-	Virus	<i>Rhinovirus</i>	Lung	[81-83]
	-		<i>Respiratory syncytial virus</i>	Lung	[84,85]
	+/-		<i>Influenza</i>	Lung	[79,80]
	+/-	Fungi	<i>Cryptococcus neoformans</i>	Lung	[76,77,87]
	-		<i>Alternaria alternata</i>	Lung	[86]
	+	Parasites	<i>Trichinella spiralis</i>	Intestine	[34]
	+		<i>Trichuris muris</i>	Intestine	[35]
	+		<i>Heligmosomoides polygyrus</i>	Intestine	[32]
	+		<i>Nippostrongylus brasiliensis</i>	Intestine/lung	[30,31,72,73]
	+		<i>Strongyloides venezuelensis</i>	Intestine/lung	[33,71]
	+		<i>Litomosoides sigmodontis</i>	Lung	[74]
	+		<i>Schistosoma haematobium</i>	Blood	[36]
ILC3	+	Bacteria	<i>Commensal microbiota</i>	Intestine	[15,24,47,49,54,62-64]
	+		<i>Citrobacter rodentium</i>	Intestine	[18,21-23,50,52,61]
	+		<i>Escherichia coli K1</i>	Intestine	[26]
	+		<i>SFB</i>	Intestine	[55,65]
	+		<i>Lactobacilli</i>	Intestine	[56]
	+		<i>Alcaligenes</i>	Intestine	[9,10]
	+/-		<i>Salmonella enterica</i>	Intestine	[25]
	+/-		<i>Salmonella typhimurium</i>	Intestine	[29,60]
	+/-		<i>Helicobacter typhlonius</i>	Intestine	[53]
	+		<i>Streptococcus pneumoniae</i>	Lung	[88,90]
	+		<i>Pseudomonas aeruginosa</i>	Lung	[89]
	+		<i>Klebsiella pneumoniae</i>	Blood	[26]
	+	Virus	<i>Rotavirus</i>	Intestine	[28]
	+	Fungi	<i>Candida albicans</i>	Lung	[89]
	+	Parasites	<i>Toxoplasma gondii</i>	Intestine	[27]

241

242

243 **Conflict of interests**

244 We declare no conflicts of interests

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507 **Legends to figures**

508

509 **Figure 1.** The activation of innate lymphoid cells. The three types of ILCs are promptly  
510 activated by distinct types of threats. Such threats are detected by myeloid and non-  
511 hematopoietic cells, which express inducer cytokines (in boxes). In reaction to inducer  
512 cytokines, ILCs express effector cytokines that both activate defense mechanisms and  
513 regulate immunity.

514

515 **Figure 2.** The control of microbiota and pathogens by ILCs. The response of ILCs to  
516 symbiotic microbes and pathogens have been extensively described in the intestine and lung,  
517 to include bacteria, viruses, fungi and parasites, as well as viruses in the liver. Given their  
518 prompt activation, ILCs play a critical role early in the effector response to perturbations in  
519 the microbiota and to pathogens, and in the regulation of adaptive immunity. In some cases,  
520 however, the reactivity of ILCs contributes to pathology.

521

522

**Figure 1**

**Intracellular threats**  
(Tumors, viruses and intracellular bacteria)



**Large parasites**  
(Helminths)



**Extracellular microbes**  
(Bacteria, fungi)



Figure 2

