CPQ Microbiology (2018) 1:4
Review

Role of Microbes and its Interaction with Innate Lymphoid System

Mukesh Verma* & Ajay Kumar Singh*

Department of Medicine, National Jewish Health, 1400 Jackson St., Denver, Colorado, USA

***Correspondence to:** Dr. Mukesh Verma & Dr. Ajay Kumar Singh, Department of Medicine, National Jewish Health, 1400 Jackson St., Denver, Colorado, USA.

Copyright

Received: 16 July 2018

Published: 09 August 2018

Keywords: *Microbes; Innate Lymphoid Cells (ILCs); Pattern Recognition Receptors (PRRs)*

Abstract

In-depth research of ILC family in immunity panel is growing rapidly. Many studies have been done to know the specific ILCs function in different sites triggering immunity, tissue repair and inflammation. Therefore, microbial interaction with ILC group which play specific roles in host homeostasis is not fully understand. A very few studies have been done in the ILC1 and ILC3 with microbial interaction but not with the ILC2s. However, ILCs have elucidated research interests in the fields of infectious immunity, inflammatory diseases, and allergic diseases. In this review we are focusing about the ILCs and how microbes interact with innate lymphocytes.

Introduction

Our immune system works with highly diverse infectious and non-infectious challenges in such a way to promotes the control of invading agents and restores the tissue homeostasis. The constitutive microbial exposure is required for the tissue-specific immunity which provides the spatial segregation from the microbiota to ensure maintenance of organ function and allow the equilibrium between tolerances to environmental antigens and regulates protective immunity [1].

These balanced are important for the protection of tissue integrity. The breakdown in tissue homeostasis results to develop the inflammatory diseases and the subsequent failure to regulate immune responses to environmental or microbial antigens [2,3]. A number of environmental cue, including infections have been raised as possible triggers.

The mammalian gastrointestinal tract is inhabited by several species of symbiotic microbes, among those some have impact on host immune system [4,5]. The microbe host interactions are involve in both innate and adaptive immune system as well as non-immunologic protective defense mechanism like mucus barrier and antimicrobial peptides (AMPs) [6]. The gut microbiota plays an important role in educating and modulating the host immune system [7]. Germ-free (GF) mice show defects in multiple specific immunocyte populations, such as Th2 skewing of their CD4+ T cell compartments; compromised innate lymphoid cell (ILC) function; a deficiency in immunoglobulin A (IgA)-producing plasma cells; and, more generally, greater susceptibility to infection [8,9]. As we know the immune system is classified as innate and adaptive immune system (humoral immunity).

What is the ILCs and Why it is Important?

Prior to advent of Innate lymphoid cells (ILCs), Natural killer cells (cNKs) represent the ILC family [10,11]. ILCs are originating from the common lymphoid progenitor and lack antigen-specific receptors [12-14]. They initiate rapid response against microbes without prior exposer. Currently, it is found that progenitor cells and surface markers of ILC family members indicate that NK cells and non-cytotoxic ILCs group do not originate from same lineage [15-18]. ILCs are found throughout the whole body but commonly reside in the skin, lung and intestine where it's participates in local immune responses and maintained the homeostatic. ILCs are divided on the basis of the expression of signature cytokines and the transcription factors that regulate their development, function and differentiation which ultimately responsible for the phenotypic distinguish.

Type of ILCs

According to a nomenclature [18] and classification system ILCs divided into three groups (Figure 1). ILC1: Which expressed transcription factor T-bet and produce Th1 type cytokines IFN-g and TNF-α; ILC2s: Which expressed transcription factors GATA3 and RORα and secrete Th2 Type cytokines IL-4, IL-5, IL-9, IL-13, and amphireguling; ILC3s: It expressed transcription factor RORyt and produce Th17 cytokines IL-17 and Il-22. Like ILC1s, natural killer (NK) cells produce IFN-y. However, NK cells also specialize in the release of lytic lysosomes containing perforin and granzymes and therefore are considered as innate counterparts of cytotoxic CD8+ T cells. ILCs also include lymphoid tissue-inducer (LTi) cells, which promote lymphoid organogenesis during development [19]. LTi cells are often considered part of the ILC3 group because they depend on RORyt for development and secretion of IL-17 and IL-22, and expressing of several cell surface markers which belong to characteristic of ILC3s. However, they may be a distinct lineage. In mouse, ILC3 are particularly diverse lineage and include fetal lymphoid tissue inducer (LTi) cells as well as three adult subsets, T-bet-CCR6+ LTi-like ILC3, T-bet+ CCR6-NKp46- (DN) ILC3, and T-bet+ NKp46+ ILC3 [20,21].

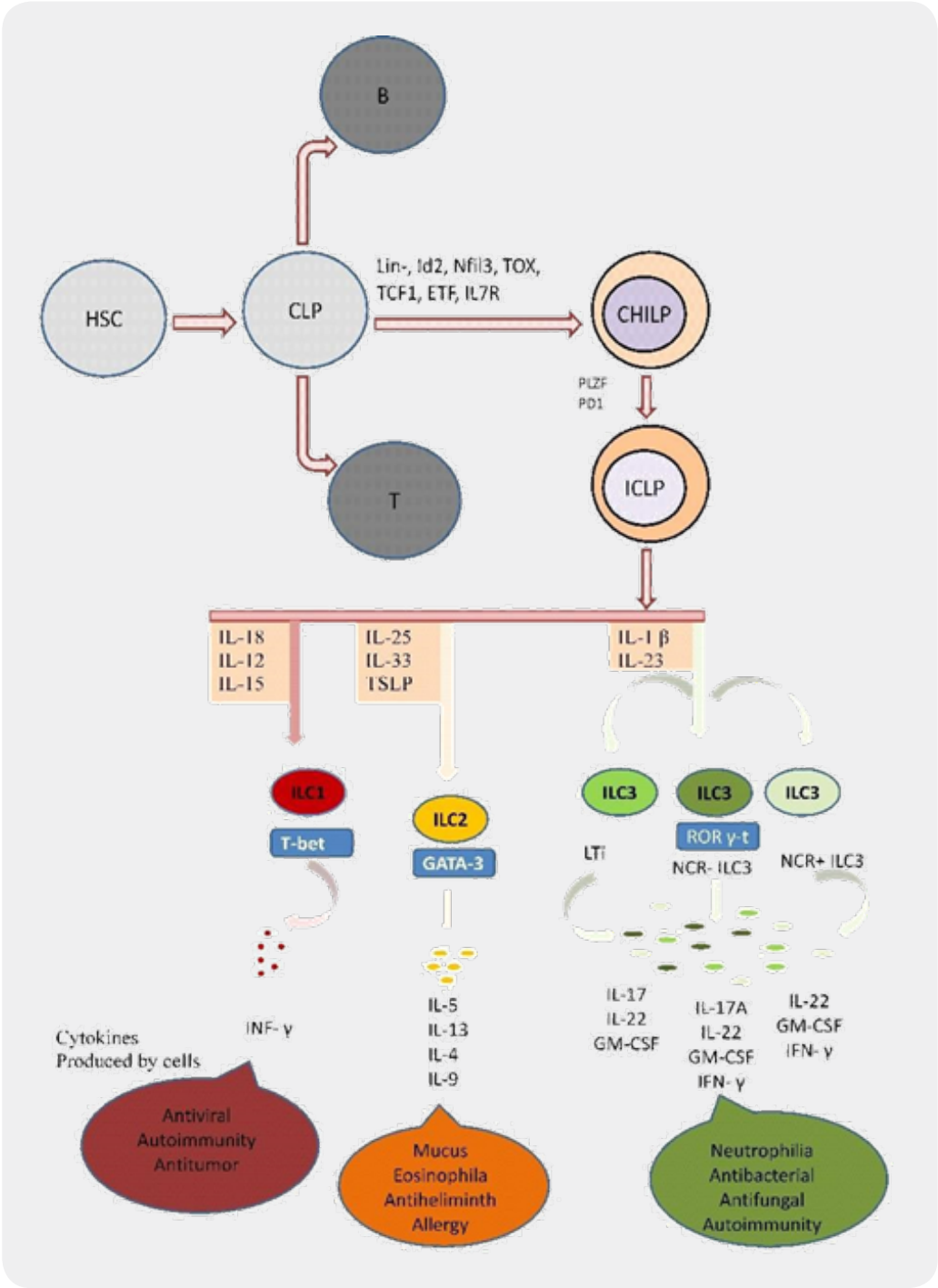

Figure 1: *Innate Lymphoid Cells (ILCs) development and differential pathway with production of signature cytokines.*

How Microbes Interacts with Innate Immune System

Both innate and adaptive immune cells utilize the defense mechanisms which work through pattern recognition receptors (PRRs). PRRs initiate responses to microbes and regulate infections. PRRs recognize the microbe-specific molecules, which called as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which are associated with components of host's cells that are released during cell damage or death [22,23]. Initial recognition of microbes through PRR, in switch to, activates cytokine and chemokine signaling pathways for anti-microbial killing (eg, antimicrobial proteins, phagocytosis, autophagy, reactive oxygen and nitrogen species). There are several subgroups of PRRs. They are classified according to their ligand specificity, function, localization and/or evolutionary relationships. Based on their localization, PRRs may be divided into membrane-bound PRRs and cytoplasmic PRRs.

1. Membrane bound PRRs involves of Toll like receptors (TLRs) and C-type lectin receptors (CLRs)

2.Cytoplasmic PRRs involves NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs).

TLR boud to ligand and tend to dimerize with different forms of dimmers. The interaction of TLRs with its specific PAMP is mediated by MyD88 pathway which triggers NF-κB or MAP kinase pathway (Figure 2). The binding of MyD88 to TLRs activates IL-1 receptor-associated kinases by MyD88, which causes downstream activation of complex containing TNF receptor-associated factor (TRAF)6 and transforming growth factor (TGF)-β-activated kinase 1. This activates TGF-β-activated kinase (TAK)-1. TAK-1 leads to the activation of both NF-κB and MAPK signaling pathways to produce pro-inflammatory and inflammatory cytokines [24,25]. CLRs induced immune response and identified as TLR-dependent and TLR-independent signaling. TLR independent signaling includes Dectin-1 and Dectin-2 signaling lead to MAP kinase and NFkB activation. NLR signaling activate inflammatory caspases causing cleavage and activation of inflammatory cytokines like IL-1activating NF-κB signaling pathway to induce inflammatory molecules. The most important members of NLRs are NOD1 and NOD2. They recognise microbial peptidoglycans in the cytoplasm and henceforth, represent different level immune responses such as TLRs and CLRs [26]. RLRs are RNA helicases, which participate in intracellular recognition of viral double-stranded (ds) and single stranded RNA which ultimately activate antiviral gene programs via N-terminal CARD domains. However they may be exploited in therapy against viral infections [27]. It has been found that antiviral program induced by RLR is based on ATPase activity. RLRs often interact with the TLRs in the innate and adaptive immune response [28].

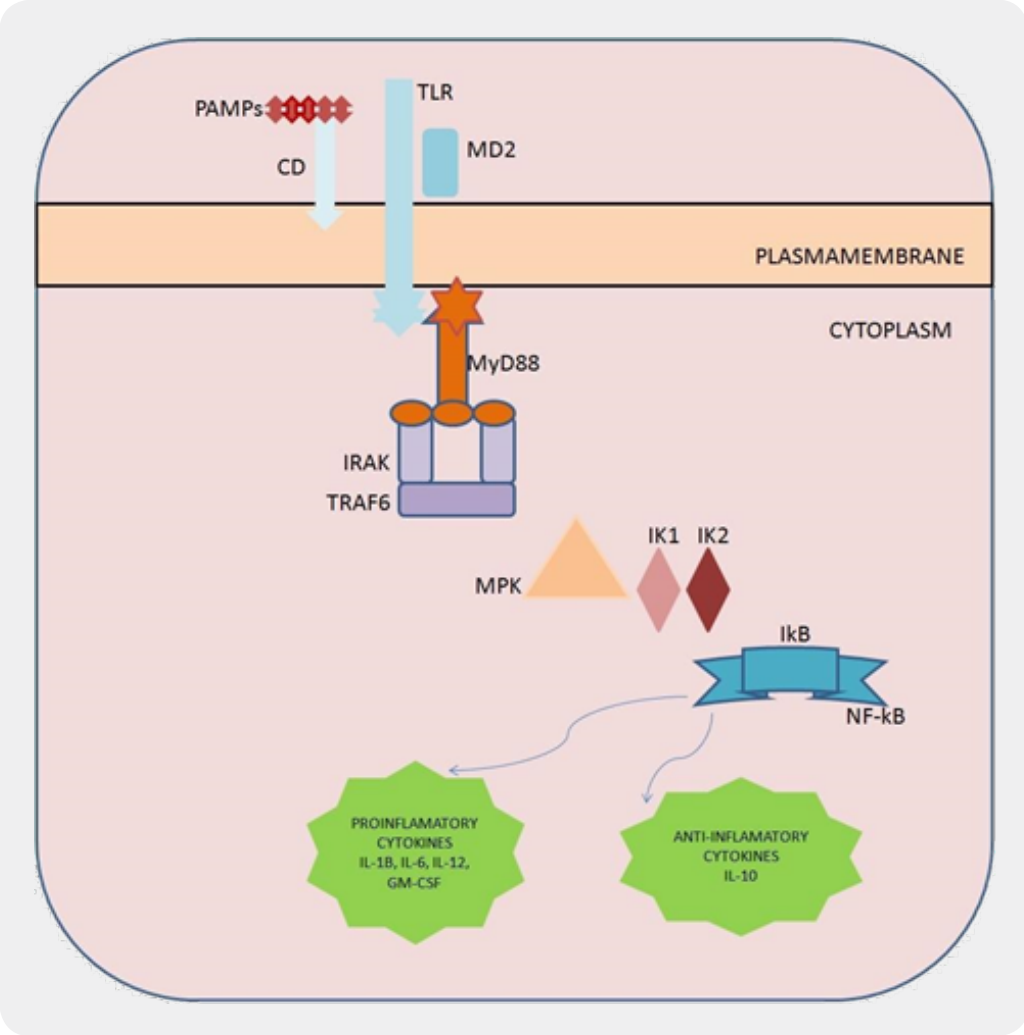

Figure 2: *Microbial generated PRR (PAMps) mediated signaling pathway for immune response.*

Known Facts About ILC and Microbes

Innate immune cells like dendritic cells (DCs) and mono-nuclear phagocytes (MNPs) interact with ILCs. Both DCs and MNPs induce IL-22 production in presence of ILC3 [29,30]. ILCs are involved in clearance of bacterial, fungal and viral infection in addition to maintenance of microbiota [31-34]. ILCs are more susceptible to microbial colonization or invasion by pathogens, such as barrier surfaces. The, microbial stimuli are dispensable for ILC3 development but necessary for Th17 cell differentiation. Moreover, ILC3s are naturally poised to secrete IL-22 in response to tissue IL-23 [35]. However, decreased numbers of ILC3s in arylhydrocarbon receptor (AHR) deficient mice result in more segmented filamentous bacteria in the microflora of the gastrointestinal tract and increased activation of Th17 cells in the attempt to decrease bacterial load [31]. Although, ILC3s act earlier than Th17 cells, the latter can override ILC3s as the adaptive response ensues, at least during primary immune responses.

Conclusion and Future Aspects

Many studies have done to know the specific ILCs function in different sites triggering immunity, tissue repair and inflammation. However, microbial interaction with ILC group which play specific roles in host homeostasis is not fully understand. Therefore, the above studies focus on how ILC responses are regulated in the presence of microbiomes. In summary, this first comprehensive description of the transcriptional and regulatory landscape of intestinal ILCs identifies high levels of diversity under conditions of homeostasis that are maintained by the commensal microbiota and that tend to an ILC3-like profile in the absence of microbial stimulation. But very few or none studied done in related to ILC2s populations which are very dominantly studies in the allergy and parasitic infection.

Author Contributions

Mukesh Verma and Ajay Kumar Singh both wrote the manuscript and equally contributed as well as responsible for editing and drafting.

Acknowledgements

I Acknowledge Ms. Judith Florence for inviting me to write an article related to my field.

Conflict of Interest

There are no conflicts of interest among authors.

Bibliography

1. Mowat, A. M. & Agace, W. W. (2014). Regional specialization within the intestinal immune system. *Nature Reviews Immunology, 14*(10), 667-685.

2. Belkaid, Y. & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. *Cell, 157*(1), 121-141.

3. Maloy, K. J. & Powrie, F. (2011). Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature, 474*(7351), 298-306.

4. Kamada, N., Seo, S. U., Chen, G. Y. & Núñez, G. (2013). Role of the gut microbiota in immunity and inflammatory disease. *Nature Reviews Immunology, 13*(5), 321-335.

5. Kau, A. L., Ahern, P. P., Griffin, N. W., Goodman, A. L. & Gordon, J. I. (2011). Human nutrition, the gut microbiome and the immune system. *Nature, 474*(7351), 327-336.

6. Hooper, L. V., Littman, D. R. & Macpherson, A. J. (2012). Interactions between the microbiota and the immune system. *Science, 336*(6086), 1268-1273.

7. Mazmanian, S. K., Liu, C. H., Tzianabos, A. O. & Kasper, D. L. (2005). An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell, 122*(1), 107-118.

8. Surana, N. K. & Kasper, D. L. (2014). Deciphering the tete-a-tete between the microbiota and the immune system. *The Journal of clinical investigation, 124*(10), 4197-4203.

9. Hepworth, M. R., Monticelli, L. A., Fung, T. C., Ziegler, C. G., Grunberg, S., Sinha, R., Wherry, E. J., *et al.* (2013). Innate lymphoid cells regulate CD4+ T-cell responses to intestinal commensal bacteria. *Nature, 498*(7452), 113-117.

10. Yokoyama, W. M. (2005). Natural killer cell immune responses. *Immunologic research, 32*(1-3), 317-325.

11. Chijioke, O. & Münz, C. (2013). Dendritic cell derived cytokines in human natural killer cell differentiation and activation. *Frontiers in immunology, 4*(365).

12. Diefenbach, A., Colonna, M. & Koyasu, S. (2014). Development, differentiation, and diversity of innate lymphoid cells. *Immunity, 41*(3), 354-365.

13. Eberl, G., Colonna, M., Di Santo, J. P. & McKenzie, A. N. (2015). Innate lymphoid cells: A new paradigm in immunology. *Science, 348*(6237).

14. Klose, C. S. & Artis, D. (2016). Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. *Nature immunology, 17*(7), 765-774.

15. Constantinides, M. G., McDonald, B. D., Verhoef, P. A. & Bendelac, A. (2014). A committed precursor to innate lymphoid cells. *Nature, 508*(7496), 397-401.

16. Klose, C. S., Flach, M., Möhle, L., Rogell, L., Hoyler, T., Ebert, K., Domingues, R. G., *et al.* (2014). Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. *Cell, 157*(2), 340-356.

17. Artis, D. & Spits, H. (2015). The biology of innate lymphoid cells. *Nature, 517*(7534), 293-301.

18. Spits, H., Artis, D., Colonna, M., Diefenbach, A., Di Santo, J. P., Eberl, G., Powrie, F., *et al.* (2013). Innate lymphoid cells-a proposal for uniform nomenclature. *Nature Reviews Immunology, 13*(2), 145-149.

19. Bar-Ephraïm, Y. E. & Mebius, R. E. (2016). Innate lymphoid cells in secondary lymphoid organs. *Immunological reviews, 271*(1), 185-199.

20. Serafini, N., Vosshenrich, C. A. & Di Santo, J. P. (2015). Transcriptional regulation of innate lymphoid cell fate. *Nature Reviews Immunology, 15*(7), 415-428.

21. Robinette, M. L. & Colonna, M. (2016). Immune modules shared by innate lymphoid cells and T cells. *Journal of Allergy and Clinical Immunology, 138*(5), 1243-1251.

22. Abraham, C. & Medzhitov, R. (2011). Interactions between the host innate immune system and microbes in inflammatory bowel disease. *Gastroenterology, 140*(6), 1729-1737.

23. Clarke, T. B. (2014). Microbial programming of systemic innate immunity and resistance to infection. *PLoS pathogens, 10*(12), e1004506.

24. Kumar, H., Kawai, T. & Akira, S. (2011). Pathogen recognition by the innate immune system. *International reviews of immunology, 30*(1), 16-34.

25. Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K. & Walter, P. (2002). The cell cycle and programmed cell death. *Molecular biology of the cell, 4,* 983-1027.

26. Caruso, R., Warner, N., Inohara, N. & Núñez, G. (2014). NOD1 and NOD2: signaling, host defense, and inflammatory disease. *Immunity, 41*(6), 898-908.

27. Pattabhi, S., Wilkins, C. R., Dong, R., Knoll, M. L., Posakony, J., Kaiser, S., Bedard, K. M., *et al.* (2015). Targeting innate immunity for antiviral therapy through small molecule agonists of the RLR pathway. *Journal of virology, 90*(5), 2372-2387.

28. Loo, Y. M. & Gale Jr, M. (2011). Immune signaling by RIG-I-like receptors. *Immunity, 34*(5), 680-692.

29. Mielke, L. A., Jones, S. A., Raverdeau, M., Higgs, R., Stefanska, A., Groom, J. R., Bracken, A. P., *et al.* (2013). Retinoic acid expression associates with enhanced IL-22 production by γδ T cells and innate lymphoid cells and attenuation of intestinal inflammation. *Journal of Experimental Medicine, 210*(6), 1117-1124.

30. Satoh-Takayama, N., Serafini, N., Verrier, T., Rekiki, A., Renauld, J. C., Frankel, G. & Di Santo, J. P. (2014). The chemokine receptor CXCR6 controls the functional topography of interleukin-22 producing intestinal innate lymphoid cells. *Immunity, 41*(5), 776-788.

31. Qiu, J., Guo, X., Zong-ming, E. C., He, L., Sonnenberg, G. F., *et al.* (2013). Group 3 innate lymphoid cells inhibit T-cell-mediated intestinal inflammation through aryl hydrocarbon receptor signaling and regulation of microflora. *Immunity, 39*(2), 386-399.

32. Powell, N., Walker, A. W., Stolarczyk, E., Canavan, J. B., Gökmen, M. R., *et al.* (2012). The transcription factor T-bet regulates intestinal inflammation mediated by interleukin-7 receptor+ innate lymphoid cells. *Immunity, 37*(4), 674-684.

33. Hernández, P. P., Mahlakõiv, T., Yang, I., Schwierzeck, V., Nguyen, N., *et al.* (2015). Interferon-λ and interleukin 22 act synergistically for the induction of interferon-stimulated genes and control of rotavirus infection. *Nature immunology, 16*(7), 698-707.

34. Gladiator, A., Wangler, N., Trautwein-Weidner, K. & LeibundGut-Landmann, S. (2012). Cutting edge: IL-17–secreting innate lymphoid cells are essential for host defense against fungal infection. *The Journal of Immunology, 190*(2), 521-525.

35. Cella, M., Fuchs, A., Vermi, W., Facchetti, F., Otero, K., *et al.* (2009). A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature, 457*(7230), 722-725.