Sepsis is a life-threatening syndrome caused by a dysregulated host response to infection, resulting in very high mortality. Dysfunction of the tightly regulated immune response occurs when the body exerts an exacerbated hyperinflammatory response that is counteracted by an anti-inflammatory response, which results in immune paralysis if it is sustained for long.

Innate lymphoid cells (ILCs) are immune effector cells of lymphoid origin that are devoid of recombination-activating gene-dependent rearranged antigen receptors, as in T and B cells. This evolutionary adaptation eliminates the necessity for antigen presentation to activate these cells, and therefore, these cells can rapidly sense and respond to infection and inflammation. ILCs sense tissue injury and pathogen infiltration through numerous cytokine, chemokine, and pattern recognition receptors. ILCs are of lymphoid origin and arise from a common lymphoid progenitor (CLP). Since ILCs share several common features with T cells, the evolutionary model suggests that ILCs are the primordial T-cell precursor. The requirement for the transcriptional repressor ID2 in the development of ILCs suggests that these cells might have originated from a common ID2-dependent progenitor. Recently, ILCs have been categorized into Group 1, Group 2, and Group 3 ILCs with different subsets in each group (Fig. 1). A subpopulation of ILCs called ILC regulatory cells (ILCregs) has been identified, and these cells are functionally similar to T regulatory cells (Tregs).

ILCs are colocalized with adaptive lymphocytes in lymphoid tissues, and a high degree of interaction between these cells is seen throughout the lifetime of an individual. Acute injuries, such as sepsis, trauma, and cardiac arrest, are associated with biological modifications in circulating lymphocyte subsets, including ILCs. During the initial phase of septic syndrome, myeloid cells cause protracted hyper- and hypoinflammatory responses, creating a distinct cytokine milieu. A significant contribution to this cytokine profile may also be due to the ILC response, leading to host defense, homeostasis, and tissue repair. ILCs respond rapidly to microbial and parasitic infections. Although the initiation and effector functions are similar to those of myeloid innate cells and helper T cells, respectively, the regulation, inhibition, and termination of the ILC response follow mechanisms different from those of other adaptive and innate immune cells. Therefore, a derailment at any phase of an ILC response may also elicit a septic episode or worsen an already-active sepsis syndrome to septic shock and Multiple Organ Dysfunction Syndrome (MODS). The possible route through which ILCs lead to a dysregulated host response is depicted in Fig. 1.

Group 1 ILCs are characterized by their ability to produce IFNγ. The members of this group are NK cells and noncytotoxic ILC1s. Cytotoxic NK cells and their development from the CLP are regulated by the inflammatory cytokine IL-15. During an infection, IL-15 expression is upregulated by all antigen-presenting cells and epithelial cells at the site of injury. This stimulus primes the differentiation of CLPs to become NK cells. The differentiated NK cells under the influence of IL-12 and IL-18 release IFNγ. Noncytotoxic ILC1s are tissue-resident cells. The intestinal microbiome normally induces epithelial cells to secrete IL-7, leading to switching of ILC3s to the ILC1 phenotype (Fig. 1). Depending upon environmental and microbial challenge, the failure of this plasticity causes a breach in the mucosal layers, leading to bloodstream infection. The release of IFNγ from the subsets of Group 1 ILCs leads to the production of Th1-inducing cytokines. In normal individuals, the IFNγ level subsides 24 h after secretion. Any disruption in the associated regulatory mechanisms, leading to persistent IFNγ-mediated hyperinflammatory response, is detrimental to the host. Evidence shows that newborns ingest ILCs through breast milk, of which ILC1s are the largest population, and IFNγ levels are much higher in breast milk compared with those of other cytokines. This is thought to shape the oral and intestinal microbiome of infants to adapt them to the real world after the sterile uterine environment. Thus, ILC1s may have a significant role in neonatal sepsis.

Group 2 ILCs are type-2 cytokine-producing cells that develop from the ILC precursor when stimulated by IL-7. ILC2s are mostly found in gut-associated lymphoid and fat tissues and in airway barriers. These cells express receptors for IL-33 and IL-25. During microbial challenge, IL-25 is released from a unique population of tuft cells in the gut and brush cells in the airways. Upon activation with IL-25, ILC2s produce IL-4, IL-5, IL-6, IL-9, and IL-13 (Fig. 1b). The released IL-4 induces the differentiation of T helper cells and the proliferation and class switching of B cells. IL-9, along with IL-13, IL-5, and IL-4, promotes the secretion of mucus, eosi

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Cellular & Molecular Immunology (2020) 17:1114–1116; https://doi.org/10.1038/s41423-020-0383-1

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SPRINGER NATURE

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Received: 6 February 2020 Accepted: 8 February 2020
Published online: 4 March 2020

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tyrosine kinase that restores lung airway epithelial integrity in sepsis. ILC2s also promote macrophage activation and antigen presentation to CD4+ T cells. In addition to the well-known involvement of ILC2s in helminth and nematode clearance, these cells play a cardinal role in organ dysfunction during sepsis. Since ILC2s promote both Type 1 and Type 2 immune responses, their involvement in sepsis depends on other immune cells (myeloid and lymphoid) that are activated by them, and the cytokine–chemokine constitution of the tissue microenvironment. ILC2s are closely associated with enteric nerves, providing an anatomical neuroimmune synapse for interactions via neurotransmitters and neuropeptides. The involvement of the enteric nervous system in modifying sepsis syndrome is well studied, and new findings suggest that ILC2s may be mediators that facilitate neuronal control of sepsis.

Group 3 ILCs are functionally characterized by their ability to secrete IL-17 and/or IL-22 cytokines upon stimulation. The major subtypes in this group are lymphoid tissue inducer (LTI) cells and ILC3s. LTI cells have a fetal origin, migrate to lymphoid structures before birth, and are committed to organogenesis of secondary and tertiary lymphoid tissues throughout life. ILC3s appear in the intestinal tract within the first 2 weeks after birth, and predominantly reside in the gut and epithelial barrier of the airway to maintain a delicate balance between the intestinal and mucosal microbiota and the immune system. ILC3s are a phenotypically diverse ILC population, and show a very high degree of plasticity that depends on changes in the local tissue microenvironment. In response to IL-2 and IL-23, ILC3s acquire the ILC1 phenotype and produce IFNγ (Fig. 1). This bidirectional switching between ILC3s and ILC1s is not thoroughly understood. ILC3s act as an early source of IL-22 and IL-17. Both of these proinflammatory cytokines provide protective immunity against several pathogens, but also have deleterious effects due to recruitment of PMNs in neonatal sepsis. Proinflammatory mediators such as GM-CSF and IL-8 help to recruit these cells. Another distinguishing characteristic is that ILC3s present antigens in MHC class II molecules, but the absence of costimulatory molecules can induce T-cell anergy. Thus, ILC3s negatively regulate elevated CD4+ T-cell activation and response to commensals. In contrast, ILC3s also activate NK and T cells by lipid antigen presentation, which is instrumental for the survival of the host in a Staphylococcus infection. ILC3s also induce and maintain the Treg population, and modulate the adaptive immune response. ILC3s adopt several mechanisms to effectively activate and regulate different arms of adaptive and innate immune responses by secreting immune mediators (IL-8, TNFα, and GM-CSF), cell contact, and antigen presentation. Most of these mechanisms are
protective to the host and commensal organisms, whereas during sepsis, dysregulation leads to accelerated apoptosis and functional defects in effector cells (Fig. 1). On the other hand, LTi cells orchestrate the generation of lymph nodes, mediate the interaction of lymphocytes in the follicles, and facilitate the survival of memory helper T cells. This multidimensional functionality of Group 3 ILCs is more pronounced in the health and disease of immunocompromised subjects, and seems to play regulatory roles during immunosuppression and immune paralysis associated with sepsis.

Recently discovered regulatory ILCs (ILCregs) represent an additional group 4 ILC. ILCregs are a novel subset of ILCs that produce IL-10 and TGFβ in response to IL-2 (Fig. 1). ILCregs are phenotypically different from Tregs, but have common functionality. ILCregs can be identified by the expression of Lin−CD45+CD127+IL10+ and the absence of FoxP3 and CD4. Studies have shown that ILCregs inhibit the stimulation of ILC1s and ILC3s through the secretion of IL-10 and TGFβ during sepsis, antagonizing the Th1 response by inhibiting IFNγ production.

In summary, cytokines activate ILCs when tissue homeostasis is disturbed. ILCs serve as key regulators and effectors of the immune response at different stages during sepsis. According to current understanding, apart from cytokine production, ILCs directly interact with T cells to shape the immune response during sepsis. More information about the role of ILCs in sepsis is forthcoming. This may open up new avenues in targeting ILCs for therapeutic intervention in sepsis.

ADDITIONAL INFORMATION
Competing interests: The authors declare no competing interests.

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