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Regulatory Innate Lymphoid Cells: A New Subset of Innate Immune Lymphocytes with More Potential Functions to be Discovered in Immune Regulation.

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Abstract:

Regulatory innate lymphoid cells (ILCregs) are a newly identified subset of innate immune lymphocytes. The discovery of this subset cell has revealed several inhibitory and stimulatory pathways that affect the regulatory functions of ILCregs, in addition to miRNA and other genetic molecular regulations. These pathways may play important roles in the pathogenesis and potential immunotherapy in patients with different kind of diseases, such as inflammation and ischemia / reperfusion injury of the kidney, acute myeloid leukemia, through immunomodulatory and anti-inflammatory pathway, as well as miRNA regulations. Further studies on ILCregs may be a potentially high interest in the near future.

Keywords: Regulatory innate lymphoid cell, ILCregs; Immune regulation

Introduction:

Innate lymphoid cell (ILCs) is a kind of innate immune lymphocyte discovered in past decade. These cells exist mostly in intestinal mucosal tissue and express no lymphoid differentiation lineage negative (Lin−) markers and antigen-specific receptors that make them distinct from T cells or B cells.[1] ILC had been a popular research interest in the past years. Interestingly, a new subset of ILCs named regulatory innate lymphoid cells (ILCregs) had been discovered recently and this may bring more research interest on the ILCs. In this review, we summarize the most recent studies on the ILCregs.

ILC subset classification:

ILCs are classified into 3 groups based on their transcription factors and cytokine production patterns which mirror helper T-cell subsets: ILC1,

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ILC2, and ILC3 subsets. Group 1 is comprised of natural killer (NK) cells and ILC1s, group 2 is comprised ILC2, and group 3 is comprised of ILC3.[2,3,4,5]

ILC2 and Th2 cells have many similarities. Both can secrete IL-4, IL-5, IL-9, IL-13 and other Th2 cytokines under the stimulation of IL-33, IL-25 and TSLP, which are mainly involved in anti-parasite infection and closely related to the occurrence of anaphylaxis. ILC3 is a group of cells expressing NKp46, but different from NK cells. ILC3cells produce IL-17 and IL-22 and are analogous to Th17 cells. Recent studies have found that ILC has protective effects on intestinal tissue damage after experimental radiotherapy and chemotherapy. ILC3 cells and IL-22 can promote the regeneration of intestinal stem cells and protect the ecological environment of stem cells. In addition, in leukemia patients receiving HSCT, the use of activated ILC3 cells before transplantation can reduce the incidence of acute GVHD.[6,7,8] ILC1 cells produce IFNγ and are analogous to T helper cells. ILC1 in human can also be divided into three subtypes according to its distribution and expression markers: type 1 of ILC1 exists in the intestinal lamina propria, expressing CD127, CD161 and T-bet, not CD56, CD94, EOMES, Granzyme and perforin; type II of ILC1 exists in intestinal epithelium and tonsil, expressing CD56, CD103, EOMES and perforin, with many characteristics of NK cells; the type III of ILC1 exists in the liver, expressing CD56, CD49a, T-bet, not CD127. It can produce perforin, and has the characteristics of NK cells and ILC1.[2,3,4] Among these ILC subtypes, NK-like type cells in ILC1 are similar to killer T cells, while other types of ILC are similar to auxiliary T cells. According to the characteristic cytokines they secrete, they respectively mediate different immune responses and participate in different physiological and pathological processes.

ILCregs: to be or not to be:

In 2017, Wang et al found a group of ILC cells of Lin-CD45 + CD127 + IL-10 + in mice and human intestines and named them regulatory innate lymphoid cells (ILCregs).[9,10] These cells are not Tregs because they do not express CD4 and Foxp3. Instead, they express ILC markers such as CD25 (IL-2R α) CD90 (THY1), IL-2R γ and Sca-1, but do not express ILC1 markers (NK1.1, NKp46), ILC2 markers (ST2 and klrg1), ILC3 markers (NKp46, CD4, and ROR γ T) and other white blood cell markers. They are a new group of ILC by secretion of L-10 and therefore named as ILCregs. The highest proportion of ILCregs in the lamina propria of small intestine measured by flow cytometry method was 13.1% and 15.7%, in mice and human, respectively, which was verified by immunofluorescence and immunohistochemistry.[9,10]

Wang et al also confirmed that ILCregs continued to express TGFBR1, tgfbr2, il2rb, and IL2RG, suggesting that ILCregs could respond to TGF-β and IL-2 signals. IL-10 and TGF-β1 were highly expressed in human ILCregs. ILCregs have different origins from ILC1-3, so ILCregs are different from Tregs and other ILCs. ILCregs has been proved to be helpful for the remission of inflammatory bowel disease. ILCregs infusion can prevent congenital colitis, Rag1 -/-IL10 -/- mice, and amplified in DSS-stimulated models. The production and amplification of ILCregs can be induced by intestinal inflammatory reaction, reaching the peak on the 8th day of stimulation, approaching the peak of inflammation. ILCregs can produce IL-10 and TGF-β1 after amplification, inhibit the activation of ILC1s and ILC3s by secreting IL-10, inhibit the secretion of cytokines IFN-γ and IL-17 by ILC1s and ILC3s, and inhibit the innate immune response. Autocrine TGF-β1 maintains the survival and expansion of ILCregs in the innate immune response of the body.[9,10]

Recent studies have also found that regulatory innate lymphocytes exist in human and mouse kidneys, expressing similar surface markers, and forming a similar proportion of total renal innate lymphocytes. In addition, IL-2, IL-7 and TGF-β were used to amplify the regulatory innate lymphocytes of kidney in vitro. These cells secrete IL-10 and TGF-β to inhibit the innate immune cells. The treatment with IL-2 / IL-2 antibody complex (IL2c) can promote the expansion of regulatory innate lymphocytes in vivo and prevent rag -/- from lack of adaptability including Tregs Renal ischemia/reperfusion injury in

mice with immune cells. The protective effect of IL2c on rag -/- mice was eliminated by the depletion of anti-CD25 antibody. Prior to or after the induction of ischemia / reperfusion injury, adoptive infusion of proliferated regulatory innate lymphocytes in vitro can improve renal function and reduce histological damage, which is related to the reduction of neutrophil infiltration and the induction of renal repair M2 macrophages. These results demonstrated that regulatory innate lymphocytes inhibit the inflammation and ischemia / reperfusion injury of the kidney.[11]

Another study has found that retinoic acid induced IL-10 secretion by human ILC2s but not type 2 cytokines. IL-10+ ILCregs, which were converted from ILC2s by means of retinoic acid stimulation, expressed a regulatory T cell–like signature with expression of IL-10, cytotoxic T lymphocyte–associated protein 4, and CD25, with down regulated effector type 2–related markers, such as chemoattractant receptor–homologous molecule on TH2 cells and ST2, and suppressed activation of CD41 T cells and ILC2s. ILCregs were rarely detected in human nasal tissue from healthy subjects or lung tissue from saline-treated mice, but numbers were increased in nasal tissue from patients with chronic rhinosinusitis with nasal polyps and in lung tissue from house dust mite–treated mice. Enzymes for retinoic acid synthesis were upregulated in airway epithelial cells during type 2 inflammation in vivo and by IL-13 in vitro. This study showed that retinoic acid transformed ILC2s into ILCregs through a unique immunomodulatory and anti-inflammatory pathway. The interaction between airway epithelial cells and ILC2s plays an important role in the production of ILCregs.[12]

However, studies for examination of circulating ILC subsets revealed surface expression of IL-10Rα and mRNA expression of both IL-10Rα and TGF-βR1 for all ILC subsets. Stimulated ILC1 production of IFN-γ was decreased by TGF-β and not IL-10. Interestingly, ILC2s stimulated in the presence of IL-10 had a marked reduction in cytokine production of IL-5 and IL-13 while TGF-β had no efect on ILC2 cytokine production. Ex vivo activated ILC1 and ILC2 subsets were also found to be a source of the immunoregulatory cytokine IL-10, raising the potential for ILC-mediated regulation of immune cells. These findings demonstrate the differential effects of immunoregulatory cytokines IL-10 and TGF-β on activated ILC1 and ILC2 populations ex vivo. [13]

In our recently results showed that the frequency of ILCregs in AML patients was significantly lower than that in normal donors. Furthermore, the frequency of the $CD45^{+}Lin^{-}CD127^{+}IL\text{-}10^{-}$ subset was also statistically significant different between normal donors and AML patients. Subset analysis on the miRNAs with the ILCregs associated id2, id3, sox4, tgfbr1, tgfbr2, il2rb and il2rg genes showed differential expression patterns between AML patients and normal donors. These results showed that there were ILCreg defects and miRNAs differential expression in AML patients.[14] Many studies have demonstrated that different gene mutations have been found in a majority of MDS and AML patients. MDS and AML patients have different gene mutation patterns. Patients with fewer or no gene mutations had a better chance of achieving complete remission when treated with induction chemotherapy regimen. Cytogenetic and mutation tests for FLT3-ITD, NPM1 and CEBPA genes were meaningful for predicting outcomes in adult AML patients. Adverse cytogenetic abnormalities and FLT3-ITD mutation showed dismal RFS and OS.[15,16,17] Some studies have demonstrated that certain miRNAs play an important role in certain malignant diseases such as AML with NPM1+/FLT3+ mutations.[18] One of the miRNAs associated with NPM1+/FLT3+ AML, miR-10a-5p showed the most statistically significant adjusted p-value in the yield as well as the highest fold change. This miRNA had been described in patients with NPM1 mutations. It's noted that high expression levels are associated with good response to induction chemotherapy.[19] More recent studies demonstrate a role for miR-10a/b in regulating the proliferation and differentiation of HL-60 leukemic cells in vitro. [20]Other literature demonstrated that high expression of miR-338 is associated with poor prognosis in acute myeloid leukemia undergoing chemotherapy. [21]However, our results show that certain ILCregs associated miRNAs had been found in both plasma and BM cells samples either up-regulated or down-

regulated.[14] These results suggest that ILCregs associated miRNAs may play an important role in the development and function of ILCregs. Future studies in ILCreg regulation may give additional information about the role of ILCregs in the pathogenesis of AML.

However, recent studies in mice have reported the absence of an intestinal regulatory ILC population distinct from ILC1s, ILC2s, and ILC3s in three different mice bred. Instead, a low percentage of intestinal ILC2s produced IL-10 at steady state. A screen for putative IL-10 elicitors revealed that IL-2, IL-4, IL-27, IL-10, and neuromedin U (NMU) increased IL-10 production in activated intestinal ILC2s, while TL1A suppressed IL-10 production. Secreted IL-10 further induced IL-10 production in ILC2s through a positive feedback loop. Therefore, ILC2s provide an inducible source of IL-10 in the gastrointestinal tract, whereas ILCregs are not a generalizable immune cell population in mice.[22]

Conclusion: Regulatory innate lymphoid cells are a new subset of innate immune lymphocytes. Although there have not been many studies, current literature has shown that this subset cell population plays an important role in immune regulation. More studies on the potential functions of ILCregs have yet to be discovered in immune regulation.

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