We read with great interest the article by Heinrich et al. that investigated the roles of innate lymphoid cells (ILCs) and their regulatory cytokines in the hepatocellular carcinoma (HCC) tumor microenvironment (TME) (1).

The authors demonstrated a relationship between the expression of cytokines in the HCC TME and patient prognosis. The total cells and cytokines from tumor (T), non-tumor (NT), and margin (M) tissues were extracted from HCC patients. Using bulk tissue RNA sequencing and unbiased clustering, gradual changes in mRNA expression between NT, M, and T tissues were confirmed. The upregulated genes in the tumor were identified and found to be associated with poor survival using The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) cohort. Moreover, differential expression of 14 cytokines (protein level) in T and NT tissues were identified, and the corresponding transcripts were also determined to be related to survival in the TCGA-LIHC cohort. These findings indicated that HCC has certain characteristic upregulated and downregulated cytokines that may induce the immunosuppressive microenvironment. Interestingly, some of these differentially expressed cytokines, such as interleukin (IL)-1β, IL-33, and tumor growth factor (TGF)-β, have previously been reported to potentially affect the plasticity of ILCs (2,3).

Heinrich and colleagues determined the phenotype, proportion, and distribution pattern of the ILCs in HCC using flow cytometry and t-stochastic neighbor embedding analysis. The results showed that the proportion of ILCs was different in NT, M, and T tissues in HCC. Specifically, the proportion of ILC2 and the ratio of ILC2/ILC1 increased in T tissues compared to NT tissues, whereas the proportion of ILC3 decreased in the majority of patients. The patients were divided into a high and low ILC2/ILC1 group according to the proportion characteristics. Interestingly, only ILC2/ILC1high patients were found to have the abovementioned changes. The authors also confirmed the presence of a cytokine gradient, specifically for the ILC-influencing cytokines in the T and M samples, in all the different groups. A CD127− population within the Lin− cells, named the “natural killer (NK)-like cells”, was identified. These had common characteristics of NK cells and ILC1, as well as the potential for differentiating into ILC1 and ILC3. There is a good reason to believe that subsets like ILC2 and NK-like cells mainly originate from the T tissues, while NK-like cells expressing markers similar to that of NK cells mainly exist in the NT tissues. However, ILC3, as the dominant subgroup of ILCs, exist in all regions. The study also evaluated the heterogeneity of helper ILCs present in the high and low ILC2/ILC1 groups, and demonstrated that activation of ILC subgroups in the tumor was higher in ILC2/ILC1high patients,
especially in terms of ILC2. The study also performed trajectory analysis for all Lin<sup>-</sup> cells and determined the intricate plasticity between ILC subsets and NK-like cells.

Combining the available literature and the results of this study (2-4), herein, we present the potential plasticity of ILCs and their regulatory cytokines in

Figure 1 A schematic model depicting the plasticity of ILCs and related regulatory cytokines in the HCC tumor microenvironment. The plasticity of ILCs in the non-tumor, margin, and tumor microenvironments in HCC is enlarged and shown in three figures. The black arrows point in the direction of potential plasticity. The figure in the right half shows the direction of plasticity of the ILCs and their regulatory cytokines in the entire HCC microenvironment. IL-1β, IL-15, IL-23, and TGF-β may promote plasticity from NK-like cells to ILC1, while IL-33, IL-4, and IL-6 may activate ILC2 as well as promote plasticity of ILC3/1 to ILC2. An increased proportion of activated ILC2 may perform two opposite functions of reducing or improving survival in HCC via the “CXCL2-neutrophils” axis and potential cross-talk with other immune cells, respectively. ILCs, innate lymphoid cells; HCC, hepatocellular carcinoma; IL, interleukin; NK, natural killer; TGF, transforming growth factor; CD, cluster of differentiation; CXCL2, C-X-C motif chemokine ligand 2.

Finally, the authors investigated the reasons for the differences in plasticity and the composition of ILCs in the ILC2/ILC1<sup>high</sup> and ILC2/ILC1<sup>low</sup> groups. It was suggested that a variety of immune cells and cytokines in the HCC TME, including but not limited to macrophages, CD8<sup>+</sup> T cells, regulatory T-cells, and IL-33, are potential mediators of HCC outcomes.

ILCs, including “helper” ILC1, ILC2, and ILC3, as well as “cytotoxic” NK cells and lymphoid tissue inducer cells, belong to the family of innate immune cells and lack rearranged antigen-specific receptors (5). ILCs are tissue-resident cells in general and are largely concentrated at surface barriers where they play a crucial role in innate defense against pathogens, immune homeostasis regulation, and lymphoid tissue formation (6). Recently, understanding
the interaction between ILCs and tumorigenesis, tumor immunity, and immunotherapy has generated great interest (1,7-9). Indeed, ILCs have been detected in the TME of various cancers, however, their roles in tumorigenesis, especially the role of helper-like ILCs, remain unclear (6,10). Due to the challenges caused by the low abundance and heterogeneity of ILCs, there is a paucity of detailed ILC studies in the literature. Furthermore, conflicting results have been reported where some studies showed that ILCs are involved in tumor progression while others indicated that ILCs confer anti-tumor properties (11,12).

Recently, Heinrich et al. (13) explained how the ILC composition regulated by the cytokines in the TME controls the survival of HCC patients. These findings may provide an insight into the mechanism through which ILCs in the TME are involved in antitumor immunity. Moral et al. demonstrated that ILC2, stimulated by IL-33, can exert antitumor effects in pancreatic adenocarcinomas by recruiting dendritic cells and CD8+ T-cells, and can also amplify PD-1 blockade (7). Heinrich et al. showed that patients with high expression of transcriptomic signature of CD117− ILC2 cells and high ILC2/ILC1 ratio had better overall survival. Interestingly, a recent study reported negative effects of ILC2 in HCC (patients with high T/NT ILC2 ratio had poor survival), and that ILC2 might exert immunosuppression via the “CXCL2-neutrophil axis” (8). This stark difference in results may be explained by the heterogeneity of the liver TME and ILCs and the insufficient sample sizes in the studies, as well as the differences in research methodology. However, there is sufficient evidence to support the plasticity observed in hepatic ILCs and the increase in ILC2. Therefore, more in-depth mechanistic analyses are warranted. In recent year, the microbiota has also been shown to be closely related to tumor immunity and immunotherapy (14). Based on the “sentinel role” of the ILCs facing microbiota, research on ILCs-microbiota cross-talk in anti-tumor immune responses may further our understanding (15). Admittedly, our understanding of the complex network centered on ILCs in the context of specific cancers is still in its infancy. Whether the ILCs-directed plasticity is a cause or a consequence of the onset and progression of malignancy remains unclear. Considering the important roles of ILCs in the TME, thorough analyses of the cross-talk among intratumor ILCs, ILC-controlling cytokines, adaptive immunity, and antitumor immunity are warranted.

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Footnote

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