I have read the comments of reviewers carefully. The paragraphs below are the responses to the reviewers. I have also added these contents highlighted in red to the manuscript.

Reviewer #1: The mini-review on the gammadelta T cells is timely to arouse interest. However, in addition to the role of gammadelta T cells itself, the role in the context of whole immune system should be briefly provided.

Answer:

γδT cells in the immune system

As a kind of unique population, γδT cells act as a bridge between innate and adaptive immunity. Their roles in immune responses depend on many aspects, such as the existing locations, the stimuli used to activate and the period of responses[21]. Their pleiotropy, such as Th1 and Th2 phenotypes, is determined by specific stimuli and cytokines in the microenvironment, and is exhibited at different stages of immune responses[22, 23]. Most of the γδT cells are Th1 phenotype. During the early stage of innate immune response, γδT cells sense the stressed epithelial cells or DCs, then recruit innate cells, including neutrophils and macrophages, by producing IL-17 and CCL2, respectively[24]. During the middle stage of enhanced adaptive response, the interaction between γδT cells and DCs is intensive, leading to the proliferation and polarization of γδT cells and maturation of DCs[24, 25]. γδT cells regulate B cells to produce a large number of immunoglobulins in the absence of αβT cells. Meanwhile, human Vγ9Vδ2 T cells act as APCs to present antigens to CD4+T cells and CD8+T cells, initiating adaptive responses[22, 26]. Whereas, γδT cells play the opposite roles of killing macrophages and αβT cells and promoting tissue repair by producing IL-10 during the later stage[21, 24].

γδT cells are also involved in antitumor immune responses. The activated cells exert cytotoxic effect by secreting perforin, granzymes, IFN-γ, TNF-α, etc. γδT cells influence DCs and αβT cells which regulate the immune responses in killing tumor cells. The combined regimens consisting of zoledronic acid,

IL-2 and Vγ9Vδ2 T cells show promising effects in clinical trials[27].

Reviewer #2: "The role of γδT cells in liver diseases and its relationship with intestinal microbiota" is an interesting paper. Authors have treated the novel argument clearly and exhaustively. However, I think that the last paragraph (LIVER/INTESTINAL γδT CELLS AND GUT MICROBIOTA) should be expanded and deepened. In fact, the matter of intestinal microbiota appears in the title of the paper but now it takes only a little part of the whole article.

Answer:

RELATIONSHIPS BETWEEN LIVER/INTESTINAL γδT CELLS AND INTESTINAL MICROBIOTA

The microbiota played an important role in maintaining hepatic γδT17 cells homeostasis. The mechanism underlying the abovementioned phenomenon could be attributed to that lipid antigens, the component of intestinal microbiota, were presented by hepatocyte CD1d via portal vein, and activated hepatic γδT cells and produced IL-17A. The activated γδT17 cells have been identified to have the abilities of pro-inflammation and anti-infection, aggravating liver disease[84, 85]. For example, the quantity of microbiota affected γδT17 cells in the liver, thus accelerating the development of NAFLD[2]. In addition, during cholestatic liver diseases the increased intestinal permeability allowed bacterial translocation to the liver, especially *Lactobacillus gasseri*. Accordingly, hepatic γδT cells responded to the microbial stimulus to secrete IL-17A, exacerbating the cholestatic liver diseases[86]. Hepatic γδT17 cells showed an active and mature status by expressing $CD44^{high}CD62L^{--}$. A study performed on lung cancer demonstrated that the number of γδT cells in the liver decreased in the absence of commensal microbiota. Li et al[2] demonstrated that *E.coli* alone could restore hepatic γδT17 cells in a dose-dependent manner. Moreover, supplementation of γδT cells and IL-17A restored immune surveillance in antibiotic-treated mice[87].

γδT cells make up 10-30% of CD3+ T cells in the intestine of healthy

subjects[11]. γδT cells are important to maintain the homeostasis of intestinal barrier so as to kill the pathogens and prevent bacteria from translocating to the liver. The commensal microbiota residing on the epithelial surface of the gastrointestinal tract modulated intestinal mucosal γδT cells[88]. These microbiota induced-γδT cells exert their roles in many pathological processes no matter in the initial stage or in the later stage[85]. For example, IL-17A produced by γδT cells affected intestinal immunity. In addition, some studies suggested that IL-17A was protective and maintained barrier functions by regulating the tight junction protein occludin in a DSS-induced colitis model[89]. A recent study suggested that *lactobacillus breves* DM9218 directly stimulated γδT17 cells by expressing TLR2 in the colon, leading to beneficial effects on colitis[88]. Another study also suggested that the bacterial consortium markedly stimulated the proliferation of γδT17 cells in the colonic lamina propria. Specific beneficial microorganisms, such as *Bifidobacterium* and *Bacillus.spp*, promoted TLR2 expression on γδT cells, which led to enhancement of barrier functions[90]. In vitro, only the *Bacillus* strains but not *Bifidobacterium* promoted TLR2 and IL-17 expression. However, bacteria constituting the families *Prevotellaceae*, *Rhodospirillaceae*, *Flavobacteriaceae* were inversely related to γδT17 cells in the intestine. Bacteria in the family *Bifidobacteriaceae* were positively correlated with γδT17 cells[90]. The communication between intestinal epithelial cells (IEC) and γδ intraepithelial lymphocytes (IEL) relied on microbiota and served to maintain homeostasis of intestinal immunity. γδIEL depended on IL-15 produced by IEC which were stimulated by microbiota to sustain their presence and functions. In turn, γδIEL promoted IEC functions, such as maintenance of epithelial barrier and lysis of invasive pathogens. Moreover, microbial localization impacted the biological behaviors of γδIEL, for instance, enhanced cytotoxicity against deleterious bacteria[85]. Microbiota was also involved in the relationship between γδT cells and cutaneous carcinogenesis. Microbial infection made Vδ2-γδT cells reside on tissue's epithelial layers. The

Vδ2-γδT cells proliferated and secreted IFN-γ upon encountering antigens, leading to cancer cell death. On the other hand, the anti-tumor subset could be transformed into the pro-tumor subset with the help of IL-23. Because of larger intercellular space and subsequent bacterial translocation, γδT17 cells expanded, causing tumourgenesis. IL-17 also inhibited effector T cells through MDSC indirectly[85].