

Peer Review File

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Reviewer A

First, the title needs to indicate that this is a narrative review or literature review.

Second, the abstract is not informative and needs some revisions. The authors need to clarify the clinical needs for this review, how the literature was retrieved, how the information from the included studies was analyzed, what the main findings from the reviewed studies were, and comments on the limitations of prior studies and future research focuses to facilitate the corresponding clinical implications.

Third, the introduction of the main text needs to explain the clinical needs for this review topic. In addition to review what has been found, the authors need to have comments on the methodology, limitations and knowledge gaps of the studies reviewed. I suggest the authors use to a figure to summarize the mechanisms found in this review.

Fourth, please briefly describe how the related studies were searched and included. In the conclusion part, please have comments on the unaddressed issues in this research focus and suggest possible future research directions.

Finally, please consider to review several related papers:

1. Sedighzadeh SS, Khoshbin AP, Razi S, Keshavarz-Fathi M, Rezaei N. A narrative review of tumor-associated macrophages in lung cancer: regulation of macrophage polarization and therapeutic implications. *Transl Lung Cancer Res* 2021;10(4):1889-1916. doi: 10.21037/tlcr-20-1241.
2. Frade BB, Dias RB, Gemini Piperni S, Bonfim DC. The role of macrophages in fracture healing: a narrative review of the recent updates and therapeutic perspectives. *Stem Cell Investig* 2023;10:4.
3. Zhu S, Li Y, Mao Y, Li X, Gao S, Geng Y, Ma J. Development and validation of a novel M1 macrophage-related gene prognostic signature for lung cancer. *J Thorac Dis* 2023;15(3):1267-1278. doi: 10.21037/jtd-23-80.

Reply: Thank you for your critical comment, we have made revisions on the manuscript point to point according to your commentaries, and we hope the revised manuscript could meet the requirement. First, we have revised title into “Mechanisms and Characteristics of Subcapsular Sinus Macrophages in Tumor Immunity: A Narrative Review” to indicate that this study is a narrative review (Page 1, line 1-2). Second, major revisions have been made on the abstract to make it informative (Page 2, line 29-52). Third, in the introduction section, we have added the clinical needed of the study (Page 3-4, line 62-73). The methodology, limitations and knowledge gaps of the studies

reviewed have been discussed in the discussion section (Page 13-14, line 352-386). Besides, we also presented a table that summarized the mechanisms of subcapsular sinus macrophages in tumor immunity found in previous studies (Table 2). Forth, the process that the related studies were searched and included has been presented in the methods sections, and conclusions have been revised according to the requirement (Page 4, line 77-88; Page 14, line 387-395). Finally, thanks again for reviewer's kindly suggestions, we have cited the relevant paper "A narrative review of tumor-associated macrophages in lung cancer: regulation of macrophage polarization and therapeutic implications" in our manuscript.

Reviewer B

The paper titled "Mechanisms and Characteristics of Subcapsular Sinus Macrophages in Tumor Immunity" is interesting. In recent years, numerous studies have demonstrated that SCSM is correlated with favorable prognosis in patients with malignant diseases, and investigated the mechanism under the role of SCSM in tumor immunity and progression. SCSM could capture TEVs and tumor cells, cross-prime effector cells, and secrete crucial cytokines at the early stage of tumor progression. In future studies, the detailed mechanisms, models to explore SCSMs and its clinical value could be expected to be validated. However, there are several minor issues that if addressed would significantly improve the manuscript.

1)What is the structural and functional basis of how the lymph node sinus system coordinates immune responses under physiological conditions, and in inflammation and cancer? It is recommended to add relevant content.

2)What is the mechanism and the immunological functional consequences for their disruption? It is recommended to add relevant content.

3)How SCSM coordinate both innate and adaptive memory responses in the subcapsular niche can provide new opportunities to bolster immunity against pathogens and cancer? It is recommended to add relevant content.

4)What is the effect of SCSM on the NK cells accumulation and activation in response to lymph-borne viral particles? It is recommended to add relevant content.

5)The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "A narrative review of tumor-associated macrophages in lung cancer: regulation of macrophage polarization and therapeutic implications, Transl Lung Cancer Res, PMID: 34012800". It is recommended to quote the article.

6)What are the roles of SCSM in forming the pre metastatic microenvironment and maintaining metastasis? It is recommended to add relevant content.

1)What is the structural and functional basis of how the lymph node sinus system coordinates immune responses under physiological conditions, and in inflammation and cancer? It is recommended to add relevant content.

Reply 1: Thanks for your kind advice. We have added relevant content in the

manuscript about the structural and functional basis of lymph node sinus system (Page 4, line 94-101).

2)What is the mechanism and the immunological functional consequences for their disruption? It is recommended to add relevant content.

Reply 2: Thanks for your great suggestions. As we have described in the manuscript the depletion of SCSM leads to a failure to induce tolerance and an impaired immune activation in vivo model following autoantigen injection. However, the detailed mechanism and the immunological functional consequences for their disruption has not been demonstrated in tumor yet. Although the process of SCSM disruption has been discussed in viral infection, whether the immunity activation process in tumor invasion is similar to that of viral infection has not been determined yet. This study focused on the function of SCSM in tumor immunity, and therefore, we are not able to present the mechanism and the immunological functional consequences for their disruption in tumor invasion (Page 12-13, line 329-342).

3)How SCSM coordinate both innate and adaptive memory responses in the subcapsular niche can provide new opportunities to bolster immunity against pathogens and cancer? It is recommended to add relevant content.

Reply 3: Thanks again for reviewer's commentary. SCSM could coordinate both innate and adaptive memory responses and bolster immunity, through the physical barrier function and cross-presentation of antigens. In immunity against virus, SCSM could serve as a repository of viral antigen, however, whether SCSM play a similar role in tumor immunity is worth investigating. We have described in the manuscript that SCSM could serve as physical barrier and participate in the activation of CD8 T cells, and we have added relevant content in the manuscript. However, this study focused on the function of SCSM in tumor immunity, we decided not to focus the effect of SCSM in pathogen infection. In tumor invasion, we have summarized potential mechanisms of SCSM in the bolstering immunity (Page 12-13, line 324-342).

4)What is the effect of SCSM on the NK cells accumulation and activation in response to lymph-borne viral particles? It is recommended to add relevant content.

Reply 4: Thanks for reviewer's advice. As we have described in the manuscript the depletion of SCSM leads to a failure to induce tolerance and an impaired immune activation. The effect of SCSM on the NK cells accumulation and activation in response to lymph-borne viral particles could activate anti-pathogen immunity in infection. In tumor invasion, the density of SCSM is basically correlated with better prognosis, and we have also summarized several possible mechanisms and signal pathways (Page 8-10, line 207-266).

5)The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "A narrative review of tumor-associated macrophages in lung cancer: regulation of macrophage polarization and therapeutic

implications, Transl Lung Cancer Res, PMID: 34012800". It is recommended to quote the article.

Reply 5: Thank you for your valuable comment. We have made revisions in the introduction part of the manuscript to make it more comprehensive, we hope that the correction will meet with approval (Page 3-4, line 58-73). We fully agreed with the reviewer's advice, and the recommended literature has been added into citations.

6)What are the roles of SCSM in forming the pre metastatic microenvironment and maintaining metastasis? It is recommended to add relevant content.

Reply 4: Thank you for your critical comment. As we have described in the manuscript, in tumor invasion, the density of SCSM is basically correlated with better prognosis. However, the effect of SCSM is controversial in the exploration of mechanisms. Even though most studies proved an anti-tumor effect of SCSM in tumor immunity, SCSM could promote tumor metastasis through STAT3 signal pathways in melanoma as well (Page 11, line 289-297). Therefore, the specific role of SCSM in forming the pre metastatic microenvironment and maintaining metastasis requires further investigations.