Peer Review File

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Review Comment

The paper makes a well-written overview of the inflammatory molecules involved in the tumour immune microenvironment.

Comment 1: According to the literature, the role of PD-L1 is not yet completely understand and further analysis are needed. I invite the author to consider the paper of Teng et al. (Classifying Cancers Based on T-cell Infiltration and PD-L1. Michele W.L. Teng et al. Cancer Res June 1 2015 (75) (11) 2139-2145; DOI: 10.1158/0008-5472.CAN-15-0255) which shows that the balance between different molecules could affect the prognosis.

Response 1

The manuscript has been edited to portray the notions that the roles of PD-L1 are not yet fully understood, and that the prognosis in the IME may be influenced by different molecules. The following paragraph has been inserted from lines 193 to 204:

"Nonetheless, given the diverse results attained by different studies, it is a possibility that the effect of PD-1/PD-L1 in the IME may be influenced by other factors, including the presence and density of TILs, the predominant PD-L (i.e. PD-L1 vs. PD-L2) in the IME, the underlying inducer of PD-L1 expression (e.g. oncogenes), the effects of PD-1 stimulation on other immune cells expressing this receptor in the IME, and other factors, some of which are likely to still be unknown (28). It has been suggested that PD-L1 expression in the IME has a dynamic property (28), which may explain studies that have shown patient response to blockade treatment despite tumors staining negative for PD-L1 (29). Therefore, although PD1/PD-L1 expression in the tumor IME appears to be associated with poorer prognosis in NSCLC, the contradicting results from different studies suggest a more complex interaction in the IME, which warrants further studies to fully characterize the effects of PD-1/PD-L1 in the IME and any other factors that may modify its effects."

Comment 2: The author considers a well-defined population of early stage patient, in which the disease is still limited and not yet systemically. However, the risk of nodal metastasis remains high. I could be a good implementation, showing whether the cited molecules can modulate the risk ok nodal metastases.

Response 2

The primary purpose of this paper was to focus on the microenvironment within the tumor itself and did not purposefully elaborate on nodal metastasis or influencing immune factors. The immune microenvironment in the draining lymph nodes is an extensive topic on its own, which was not the focus of this paper.

Comment 3: About the risk stratification, do you think that radical resection with surgery in these early stages could be the best diagnostic tool or the simple biopsy it could be enough? Please discuss.

Response 3

In terms of analysis of the tumor IME, radical resection provides a better sample for analysis and this has been reflected in the conclusion paragraph by adding the following statement, "*Better characterization of the true IME including the tumor, and the tumoral and peritumoral stroma, is currently most suitably achieved through analysis of resected specimen*"