Reviewer's report

Title: Pancreatic adenocarcinoma exerts systemic effects on the peripheral blood myeloid and plasmacytoid dendritic cells: an indicator of disease severity?

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Reviewer: Mirella Giovarelli

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The manuscript by Vegard Tjomsland and colleagues examined the influence of ductal pancreatic adenocarcinoma (PDAC) on levels of peripheral blood dendritic cells (DCs) and inflammatory mediators in comparison to the effects exerted by other pancreatic tumors, chronic pancreatitis and age-matched healthy donors. The Authors show that all patients examined had decreased levels of myeloid DCs (MDC) and plasmacytoid DCs (PDC) and enhanced apoptosis in these cells as compared to controls. Moreover they observe elevated levels of PGE2 and CXCL8 in subject with PDAC and chronic pancreatitis. However tumor surgery do not restore the levels of DCs in the majority of patients, even if decrease the levels of CXCL8 and PGDE2, as measured 8-12 weeks after.

The Authors show the connection of longer survival time (>2 year) and level of DCs in the blood compartment in patients with PDAC and suggest that the percentage of DCs pre-surgery may be predictive of surviving of PDAC patients.

This study confirms already published data on the decreased frequencies of blood DCs in subjects with pancreatic cancers and other types of cancers. The Authors show specific data about the relative amount of circulating MDC and PDC and their proapoptotic behaviour.

The major point is the small number of PDAC patients (25) pre surgery and post surgery (16) enrolled in the study. The number of enrolled patients is too low to support final Authors conclusions. Moreover it is not clear why not all PDAC patients are considered for some analysis (see specific points below). This issue must be clarified throughout the paper. The Authors should show not only a decrease in the % of circulating DCs in blood of PDAC patients, but also an impairment in their function. There are no data about the maturation stage of these DCs, as expression of CD83, CD86, CCR5, CCR7, ecc., the ability to release IL-12 p70 or IL-10 ecc. It would be important for the study to correlate the number of circulating DCs with the number of DCs infiltrating tumor mass and the expression of proinflammatory cytokines and chemokines inside.

Minor Essential Revisions:

1) METHODS section- Flow cytometry monoclonal antibodies: How is possible to distinguish apoptotic cells by staining with Annexin V APC protein in the fraction of FITC lin-, HLA-DR PerCP, CD11c APC dendritic cells? This issue should be clarified. Perhaps Authors used other labelled Ab, that should be described.
2) Table 1: N. PDAC Patients Pre surg. are 25, but post surg. are only 16. Why 9 patients are missed?

3) RESULT section – Peripheral blood MDCS and PDCs are diminished ecc……lines 29-30: Individuals with AC do not have significant decreased levels of MDCs compared to controls. See Fig. 1B. Moreover the levels of PDCs are not significantly reduced in CP patients. See Fig. 1B . What is the survival time of those few patients that present very very low levels of MDCs and PDCs?

4) RESULT section – The blood MDCs and PDCs impairment persist ecc.: Patients in which the DCs subsets did not return to normal or even decreased post surgery had recurrence? It is difficult from Fig 2 A to appreciate the recovery or not of DCs postsurgery. More inflammation induced by the surgically procedure seems not to be a valid explanation for the absence of DCs recovery, since Fig. 5 shows no increase of PGE2 and CXCL8 in PDAC patients post surgery.

5) RESULT section – Elevated levels of apoptotic blood MDCs and PDCs in PDAC and chronic pancreatitis: PDCs and MDCs do not exhibit a further increase in the level of apoptosis after the surgery in PDAC, as shown in Fig. 4 B. This issue should be corrected and/or clarified.

6) RESULT section – Elevated PGE2 and CXCL8 in plasma from individuals with PDAC and ……: The Authors say that the CXCL8 level is significantly lowered in PDAC patients post surgery, but in Fig. 5 C-D it is not shown the significance of lower level of CXCL8 for PDAC after surgery, because in the legend to Fig.5 it is specified that the comparison is between individuals with pancreatic disease and healthy donors.

7) RESULT section – Long time PDAC survivors are presented ecc……:
As stated in Tab 1, PDAC patients pre surg. should be 25 and not 13 (7 short time survivors and 6 long term survivors). Authors should explain this discrepancy. Why are missed data about the other 12 PDAC patients evaluated throught the study? For this reason data shown in fig. 6 are not evaluable, and cannot support the conclusion that “data show the connection of longer survival time and level of DCs in the blood compartment in patients with PDAC”, because only 50% of PDAC patients were considered.

Minor points:
1. Correct throughout the paper the word “linage” in lineage
2. It is not specified if the 3 patients that present an increase of DCs post surgery had a better survival
4. Legend to fig. 3, line 5: papilla Vateri adenocarcinoma is not mentioned in Methods and is not shown in the fig. It should be deleted.
4. The manuscript should be accurately revised for typos errors.
Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'