Characterization of PD-L1 as novel therapeutic target in mastocytosis

Experimental Hematology/Oncology

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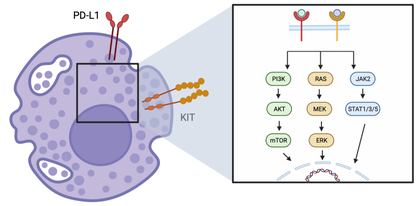
Introduction

Mastocytosis is characterized by pathological accumulation of mast cells (MC) in various tissues. Treatment options have improved in recent years, especially after approval of KIT-targeting tyrosine kinase inhibitors (TKI) in systemic mastocytosis. However, current available therapies do not have a significant effect on the malignant clone size, and many patients do not respond sufficiently. Therefore, additional treatment options are needed. In order to identify novel potential therapeutic options for mastocytosis, various biomarkers have been characterized over the past few years. Among those, the immune checkpoint ligand PD-L1 has emerged as potential novel therapeutic target in advanced systemic mastocytosis (advSM).



Conclusions

- Expression of PD-L1 on mast cells is increased in Scl-CreER;KitD814Vfl mice and its upregulation is KIT-driven.
- Treatment with anti-PD-L1 decreases numbers of mast cells in various tissues in Scl-CreER;KitD814Vfl mice.
- Expression of PD-1 on T cells is increased in Scl-CreER;KitD814Vfl mice.
- IL-10, involved in T cell death, is highly expressed in Tregs from Scl-CreER;KitD814Vfl mice.
- T cells from Scl-CreER;KitD814Vfl mice show a marked increase in effector/memory populations.

Aims of the project

1. Investigation of the expression of PD-L1 on mast cells in a mastocytosis mouse model
2. Assessment of treatment of mastocytosis mice with a PD-L1 inhibitor
3. Investigation of the expression of PD-1 on T cells in mastocytosis mice

Methods

Cells:
- Bone marrow-derived mast cells (BMMC) from SclCre;KitD814V mice

Mouse model:
- SclCre;KitD814Vfl mice

KIT and PD-L1 inhibitors:
- Avapritinib (BLU-285, KIT-specific TKI)
- Dactolisib (PI3K/mTOR inhibitor)
- Mouse anti-PD-L1 (10F.9G2)

Treatment readout:
- Flow cytometry
- Mcpt-1 ELISA assay
- Toluidine blue staining on paraffin-embedded tissue sections

Outlook

The results obtained so far *ex vivo* and *in vivo* in SclCre;KITD814Vfl mice suggest an important role of PD-L1 in mast cell processes and signaling. To extend our findings that PD-L1 can serve as suitable therapeutic target in mastocytosis, we plan to also explore the physiological role of PD-L1 in mast cells using knockout mice for PD-L1. Furthermore, the role of the PD-L1/PD-1 axis in mastocytosis will be further evaluated by depletion of T cells.

Results

1. Expression of PD-L1 is increased in mast cells from Scl-CreER;KitD814Vfl mice

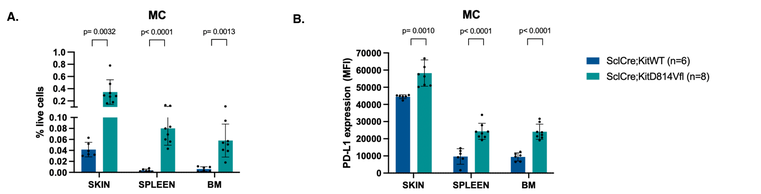


Figure 1. Analysis of mast cell number and PD-L1 surface expression on mast cells
A) Mast cells number was measured in bone marrow, spleen and skin from SclCre;KITD814V and SclCre;KITWT mice with flow cytometry. B) PD-L1 surface expression was measured in mast cells from SclCre;KITD814V and SclCre;KITWT bone marrow, spleen and skin with flow cytometry.

2. Avapritinib treatment decreases PD-L1 expression levels *in vivo* and *in vitro* in SclCre;KitD814Vfl mice

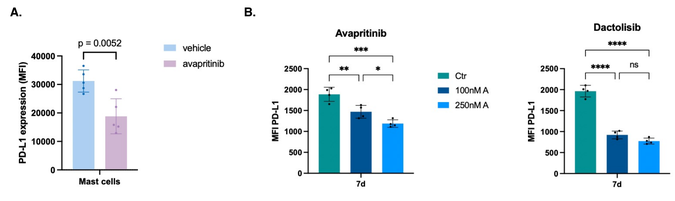


Figure 2. Analysis of PD-L1 expression after treatment with TKI inhibitor (avapritinib) *in vivo* and *in vitro*
A) PD-L1 expression on spleen mast cells was measured via flow cytometry after treatment of mice with avapritinib (30 mg/kg - oral gavage for 14 days) and respective vehicles. B) PD-L1 expression on SclCre;KITD814V BMMC was measured via flow cytometry after 7 days of treatment with avapritinib and dactolisib (PI3K-mTOR inhibitor).

3. Anti-PD-L1 treatment *in vivo* decreases mast cells number in SclCre;KITD814Vfl mice

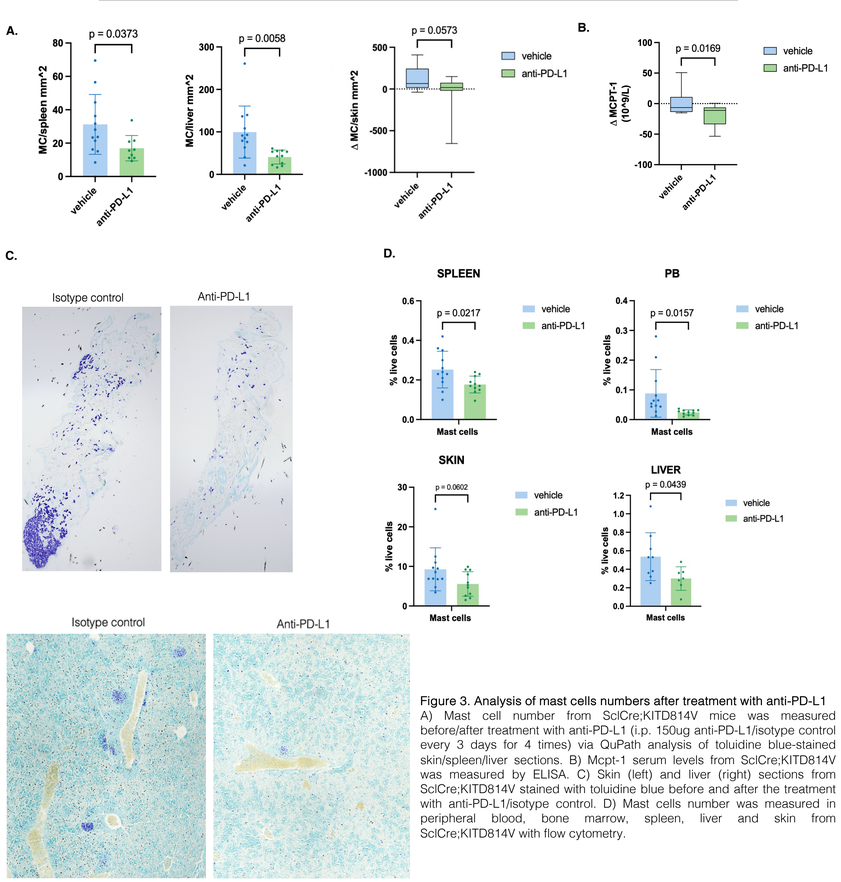


Figure 3. Analysis of mast cells numbers after treatment with anti-PD-L1
A) Mast cell number from SclCre;KITD814V mice was measured before/after treatment with anti-PD-L1 (i.p. 150ug anti-PD-L1/isotype control every 3 days for 4 times) via QuPath analysis of toluidine blue-stained skin/spleen/liver sections. B) Mcpt-1 serum levels from SclCre;KITD814V was measured by ELISA. C) Skin (left) and liver (right) sections from SclCre;KITD814V stained with toluidine blue before and after the treatment with anti-PD-L1/isotype control. D) Mast cells number was measured in peripheral blood, bone marrow, spleen, liver and skin from SclCre;KITD814V with flow cytometry.

4. Expression of PD-1 is increased in T cells from Scl-CreER;KitD814Vfl mice

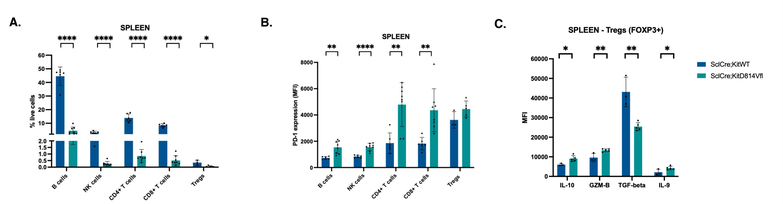


Figure 4. Analysis of spleen and bone marrow cell composition and PD-1 surface expression
A) SclCre;KITD814V and SclCre;KITWT spleen cell composition was measured with flow cytometry. B) PD-1 surface expression was measured in different cell types from SclCre;KITD814V and SclCre;KITWT spleen with flow cytometry. C) Intracellular expression levels of different cytokines were measured in spleen Tregs from SclCre;KITD814V and SclCre;KITWT mice via flow cytometry.

5. T cells from Scl-CreER;KitD814Vfl mice show a marked increase in effector/memory populations

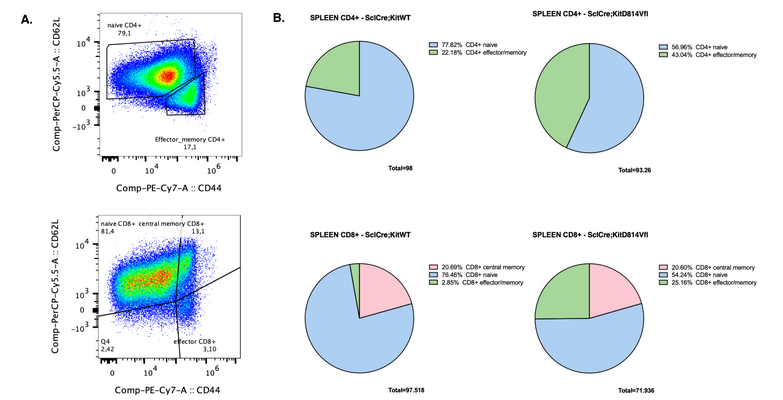


Figure 5. Analysis of T cells subpopulations in spleen and bone marrow
A) Representative dot plots showing CD4+/CD8+ splenic T cells subpopulations. B) Splenic T cells subpopulation were identified via flow cytometry after staining for CD4, CD8, CD62L and CD44.

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