SOHC
SWISS ONCOLOGY & HEMATOLOGY CONGRESS

University of Basel
Department of Biomedicine

DBM Basel

Expression of *KIT* D814V in murine hematopoietic stem cells results in an advanced mastocytosis phenotype with associated myeloid neoplasm

Experimental Hematology/Oncology

Stivala Simona[1], Alina Makeeva[1], Elena Ratti[1], Laetitia Clauss[1], Etnik Sheremeti[1], Martina Konantz[1], Karin Hartmann[1,2]
[1]Department of Biomedicine, University Hospital Basel and University of Basel, [2]Division of Allergy, Department of Dermatology; University Hospital Basel

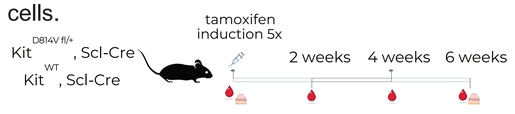
1. Introduction

Mastocytosis is a neoplasm characterized by an abnormal expansion of mast cells (MC) in one or various organs such as bone marrow (BM), skin and/or intestine. Over 90% of patients present the *KIT* D816V mutation, which results in constitutive activation of the receptor[1]. Although KIT D816V-specific inhibitors (avapritinib, bezuclastinib) reduce symptoms and prolong survival in systemic mastocytosis[2], not all patients benefit from this therapy; therefore, there is an urgent need for novel treatment options.

2. Methods

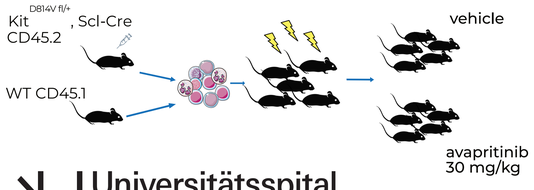
Mouse model

A knock-in mouse line carrying the D814V mutation flanked by lox-P sites was generated by CRISPR-Cas9. Mice were crossed with the Scl-Cre line to obtain tamoxifen-inducible Cre-mediated recombination in the hematopoietic system. Knock-in mice and Kit WT littermate controls were induced with intra-peritoneal tamoxifen at 6 weeks of age, followed by monitoring for peripheral blood count, survival and skin biopsies for enumeration of mast cells.



Bone marrow transplantation and *in vivo* treatment

Bone marrow cells from induced primary mice (CD45.2) were isolated, mixed in a 1:1 ratio with competitor WT cells (CD45.1) and injected intravenously into irradiated CD45.1 recipients.



Universitätsspital Basel

3. Results

Mice expressing KIT D814V in the hematopoietic compartment developed shortly after tamoxifen induction a phenotype of advanced systemic mastocytosis, more specifically systemic mastocytosis with associated hematological neoplasm, characterized by expansion of mast cells and other hematopoietic cells (leukocytes and erythrocytes), spleno-hepatomegaly and reduced survival.

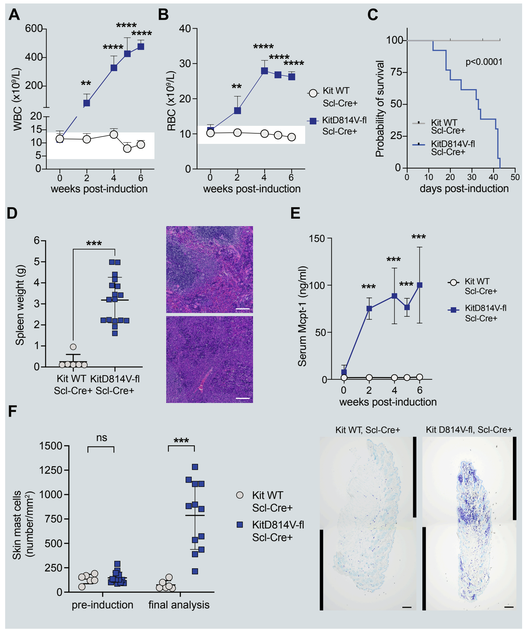


Fig.1 KitD814V-fl mice show blood leukocytosis (**A**), erythrocytosis (**B**), and a reduced survival (**C**). Spleen is enlarged with loss of the normal architecture and extramedullary hematopoiesis (**D**). Serum levels of mast cell protease-1 (Mcpt-1) are significantly elevated in mice expressing mutant Kit (**E**), and correlate with skin mast cell number (**F**). Scale bar: 100 µm.

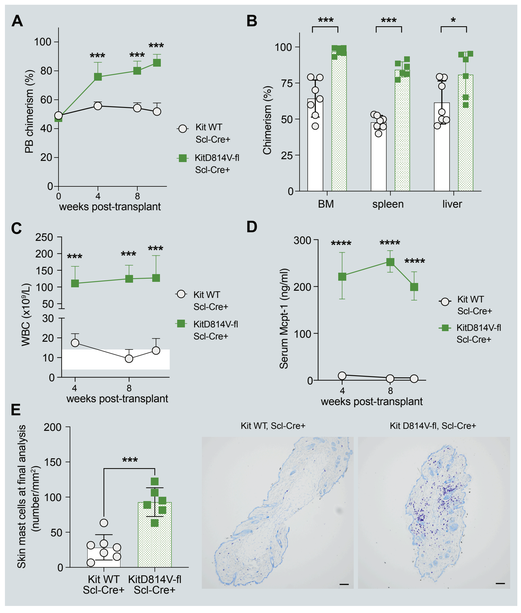


Fig.2 Hematopoietic cells carrying the Kit D814V-fl mutation show a proliferative advantage in competitive transplantation (**A**). The mutant clone is significantly expanded in BM, spleen and liver (**B**). Transplanted mice recapitulate the phenotype of the donor mouse, with leukocytosis (**C**), elevated serum Mcpt-1 (**D**) and expansion of mast cells in the skin (**E**). Scale bar: 100 µm.

Contact

Stivala Simona
simona.stivala@unibas.ch
www.biomedizin.unibas.ch

Presented at SOHC 2024 from 20-22 November 2024.

References

1. Pardanani et al., BJHaem 2023
2. Gotlib et al., Blood 2022

Conclusion

In the present study, we show that expression of *Kit* D814V in the HSC compartment leads to a phenotype closely resembling human advanced systemic mastocytosis with myeloid neoplasia. We also demonstrate that this phenotype can be corrected by treatment with the KIT inhibitor avapritinib. Thus, this novel mouse line represents an invaluable tool for elucidating molecular pathogenetic mechanisms and testing novel therapeutic targets in mastocytosis.

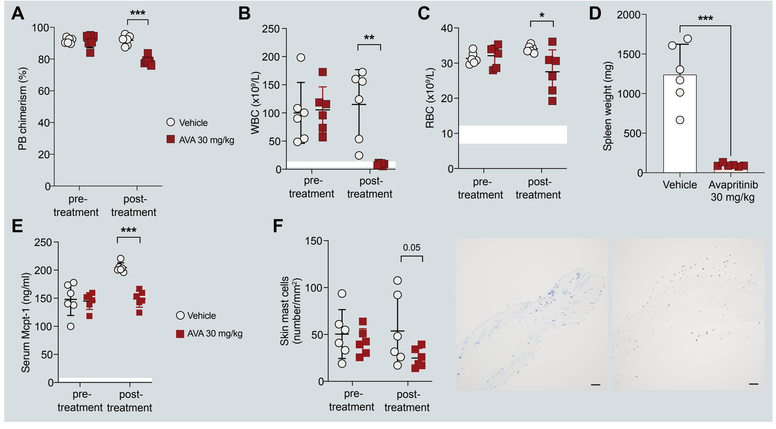


Fig.3 Mice transplanted with KitD814V-fl BM cells mixed 1:1 with Kit WT cells were randomized 8 weeks after transplantation to receive vehicle or avapritinib 30 mg/kg by oral gavage for 16 days. Treated mice showed a modest but significant reduction in peripheral blood mutant allele burden (**A**) normalization of white blood cell values (**B**) and spleen size (**D**), as well as a significant reduction in RBC values (**C**). Serum Mcpt-1 remained unaltered from pre-treatment values, while it increased in vehicle-treated mice (**E**); at the same time there was a trend for a reduction in skin mast cells (**F**). Scale bar: 100 µm.

UKBB
University Children's Hospital Basel