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Modeling Advanced Systemic Mastocytosis: An Inducible Kit D814V Mouse as a Preclinical in Vivo Platform For Therapeutic Development

Experimental Hematology / Oncology

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INTRODUCTION

Systemic mastocytosis is distinguished by the clonal expansion of mast cells (MC) across multiple organs, particularly the bone marrow and skin.[1] Although treatment options have improved, development of efficient therapies is still slow with only limited clinical trials available and absence of established pre-clinical *in vivo* models.

AIM

To generate and characterize a novel tamoxifen-inducible mouse model of systemic mastocytosis (HSC-Scl-CreER^{T};Kit^{D814Vflox}) that expresses the Kit D814V mutation (homologous to human KIT D816V)[2] in hematopoietic stem cells[3], in order to:

- Model MC expansion across multiple organs, including bone marrow and skin.
- Investigate anaphylactic responses associated with systemic mastocytosis.
- Evaluate the therapeutic potential of targeting oncogenic KIT signaling *in vivo.*

METHODS

- Disease progression in mice was monitored using skin biopsies, peripheral blood analyses, histology, and flow cytometry.
- IgE- and MRGPRX2-mediated anaphylaxis were performed as described[4] using DNP-specific IgE and ciprofloxacin, respectively.
- Additionally, diseased mice received oral avapritinib (30 mg/kg body weight, daily), a tyrosine kinase inhibitor approved for human systemic mastocytosis, and were observed for its impact on disease progression and anaphylaxis susceptibility.

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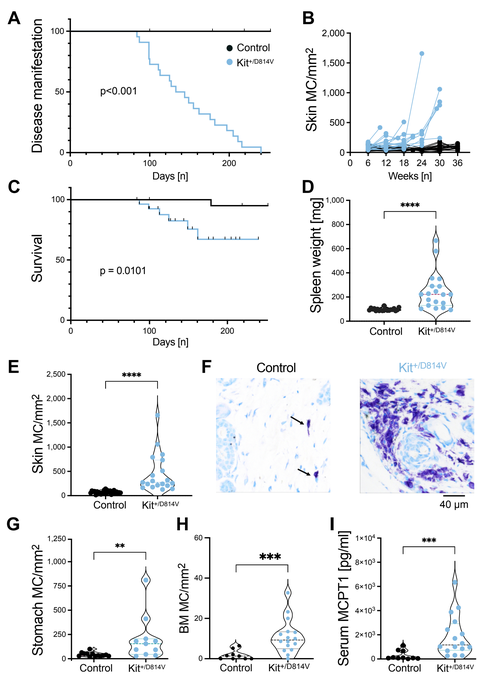
RESULTS

1. Mastocytosis phenotype in Kit$^{+/D814V}$ mice



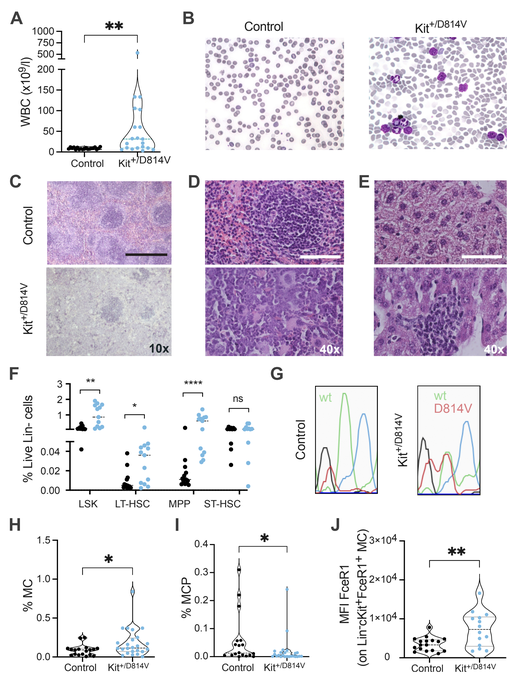
A-B. Mutant mice show signs of disease by a median of 137 days (A) and increased skin mast cells over time (B).

C-D. Kit-mutant mice have significantly reduced survival (C) and exhibit pronounced splenomegaly (D).

E-H. Increased mast cells in the skin (E,F), stomach (G) and bone marrow (H) of Kit-mutant mice at final analysis. Representative images are shown in (F).

I. Elevated serum Mast cell protease 1 (MCPT1) level in mutant mice.

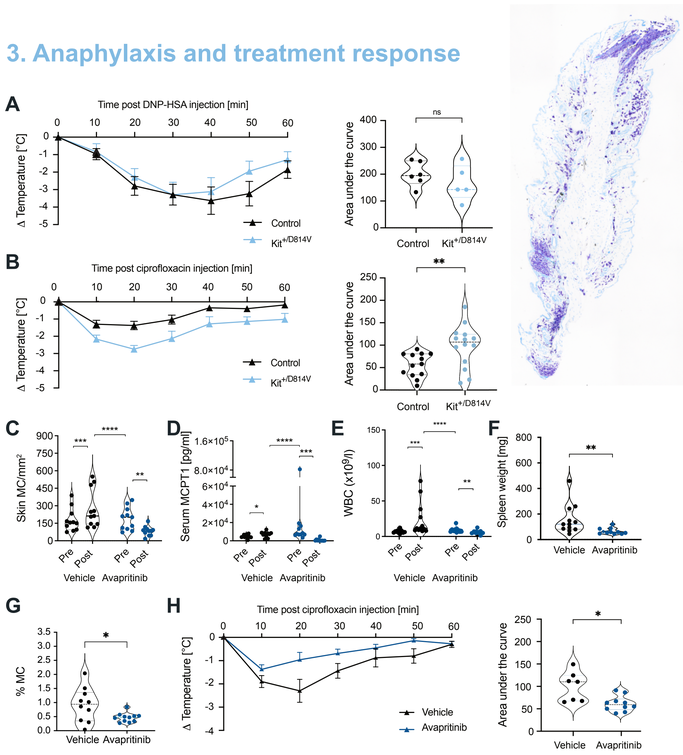
2. Associated hematopoietic neoplasm



A-E. Elevated WBC counts (A) and hematopoietic neoplasia with blast-like infiltration in the peripheral blood (B) and spleen (C, D), marked extramedullary hematopoiesis (spleen, C-D and liver, E) and tissue disruption of the spleen (C, D) in mutants.

F-J. Altered hematopoietic compartment and MC populations in Kit-mutant bone marrow. Lin-Sca1+cKit+ (LSK), LT-HSC and multipotent progenitor (MPP) frequencies are increased (F). LSK harbor the Kit D814V mutation (G). H–J) Frequencies of MC, MC progenitors (MCP), and FcεR1 mean fluorescence intensity (MFI) on MC. MC are increased (H), MCP decreased (I), and FcεR1 expression elevated (J) in Kit-mutant mice.

3. Anaphylaxis and treatment response



A-B. IgE-mediated responses are similar between groups (A), while MRGPRX2 (MrgprB2 in mice) activation via ciprofloxacin induces a stronger reaction in Kit$^{+/D814V}$ mice (B). Anaphylaxis was assessed by body temperature drop; AUC (area under the curve) was used for comparison.

C-G. Avapritinib alleviates mastocytosis. Skin MC numbers (C), serum MCPT1 (D), WBC counts (E), splenomegaly (F) and bone marrow MC burden (G) decrease after treatment.

H. Avapritinib attenuates MrgprB2-mediated anaphylaxis. Treated Kit$^{+/D814V}$ mice show a significantly reduced anaphylactic response to MrgprB2 activation compared to controls.

CONCLUSIONS

Kit$^{+/D814V}$ mice develop signs of systemic mastocytosis at a median of 137 days.

Mast cell numbers in the skin significantly increase over time in Kit$^{+/D814V}$ mice, reaching 474 MC/mm² (± 218) compared to 71 MC/mm² (± 16) in controls.

Kit$^{+/D814V}$ mice develop splenomegaly (250 mg ± 82.2 vs. 97 mg ± 5.6) and an associated hematologic neoplasm, characterized by elevated blood cell counts and the presence of immature blood cells.

Frequencies of LSK cells, hematopoietic progenitors, and mature MCs are increased in the bone marrow of mutant mice.

Treatment with the tyrosine kinase inhibitor avapritinib reduces MC counts by 61.3%, compared to a 177% increase in vehicle-treated mice. Avapritinib also significantly decreases serum MCPT1 and MC frequencies in the bone marrow, indicating reduced systemic MC burden. Furthermore, avapritinib restores blood counts and reduces splenomegaly.

Avapritinib also mitigates susceptibility to MrgprB2-mediated anaphylaxis.

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