**Supplementary Material and Methods**

**Flow cytometry**

MCs were blocked for 15 min at 4 °C with human AB-serum (Biotest, Dreieich, Germany) and incubated with antibodies for 30 min at 4 °C [1]. Anti-human MRGPRX2 (clone K125H4, Biolegend San Diego, CA, USA) was used at 0.15 µg/mL and PE-labelled mouse IgG2b-PE (clone eBMG2b, eBioscience, San Diego, CA, USA) served as isotype control. MRGPRX2 surface expression was measured on the MACSQuant (Miltenyi-Biotec, Bergisch Gladbach, Germany). Data were analyzed using the FlowJo analysis software (FlowJo LLC, Ashland, OR, USA).

**Immunofluorescence**

Suspensions of stained skin MCs (anti-human MRGPRX2 antibody, clone K125H4, Biolegend) were washed once with ice cold 1x PBS, fixed with 4% paraformaldehyde and then resuspended in 110 µl PBS for cytospin preparation. Approximately 50.000 cells were spun on a glass slide for 3 minutes at 500 rpm and covered with DAPI containing Fluoromount-GTM (Invitrogen). Photographs were taken on the BZ-X810 Keyence microscope (objective 40x) [2].

**Cell line**

The leukemic MC line HMC-1 was kindly provided by Dr. J.H Butterfield [3]. Cells were cultured at 5x105-1x106/mLin the same medium as used for skin MCs and cells were fed three times a week.

**MRGPRX2 RT-qPCR**

RT-qPCR for MRGPRX2 was performed as described in the main manuscript using the following primers, as described [2]:5’ –GGATCAGGAAGACCGGGATCA-3’ and 5’–CGGCCTGGGGAACAGAAAGT-3’.

**References**

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2. Babina, M.; Wang, Z.; Roy, S.; Guhl, S.; Franke, K.; Artuc, M.; Ali, H.; Zuberbier, T. MRGPRX2 Is the Codeine Receptor of Human Skin Mast Cells: Desensitization through beta-Arrestin and Lack of Correlation with the FcepsilonRI Pathway. *J Invest Dermatol* **2020**, 10.1016/j.jid.2020.09.017, doi:10.1016/j.jid.2020.09.017.

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