

ELKS1 controls mast cell degranulation by regulating the transcription of Stxbp2 and Syntaxin 4 via Kdm2b stabilization

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Authors

Hiu Yan Lam^{1,2}, Surendar Arumugam¹, Han Gyu Bae³, Cheng Chun Wang⁴, Sangyong Jung³, Ashley Lauren St. John^{5,6,7}, Wanjin Hong⁴, Weiping Han³ and Vinay Tergaonkar^{1,8*}

Affiliations

¹Laboratory of NF- κ B Signaling, Institute of Molecular and Cell Biology (IMCB), 61 Biopolis Drive, Proteos, Singapore 138673, Singapore.

²Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore (NUS), Singapore 117596, Singapore.

³Singapore Bioimaging Consortium, Agency for Science, Technology and Research, #02-02 Helios, 11 Biopolis Way, Singapore 138667, Singapore.

⁴Institute of Molecular and Cell Biology (IMCB), 61 Biopolis Drive, Proteos, Singapore 138673, Singapore.

⁵Program in Emerging Infectious Diseases, Duke-NUS, Singapore 169857, Singapore.

⁶Department of Microbiology and Immunology, NUS, Singapore 119077, Singapore.

⁷Department of Pathology, Duke University Medical Center, Durham, NC, USA.

⁸Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore (NUS), Singapore 119074, Singapore.

*Corresponding author

Dr Hiu Yan Lam is an IMCB Joint Student between Prof Vinay TERGAONKAR and WanJin HONG's Laboratory.

For more information on Prof Vinay TERGAONKAR and WanJin HONG's Laboratory, please refer to: <https://www.a-star.edu.sg/imcb/imcb-research/scientific-programmes/mechanisms-in-physiology-and-diseases>

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ABSTRACT

ELKS1 is a protein with proposed roles in regulated exocytosis in neurons and NF- κ B signaling in cancer cells. However, how these two potential roles come together under physiological settings remain unknown. Since both regulated exocytosis and NF- κ B signaling are determinants of mast cell (MC) functions, we generated mice lacking ELKS1 in connective tissue MCs (*Elks1^{ff} Mcpt5-Cre*) and found that, while ELKS1 is dispensable for NF- κ B-mediated cytokine production, it is essential for MC degranulation both *in vivo* and *in vitro*. Impaired degranulation was caused by reduced transcription of Syntaxin 4 (STX4) and Syntaxin Binding Protein 2 (Stxbp2), resulting from a lack of ELKS1-mediated stabilization of lysine-specific demethylase 2B (Kdm2b) which is an essential regulator of STX4 and Stxbp2 transcription. These results, for the first time suggest a transcriptional role for active-zone proteins like ELKS1 and suggest that they may regulate exocytosis through a novel mechanism involving transcription of key exocytosis proteins.

FIGURE

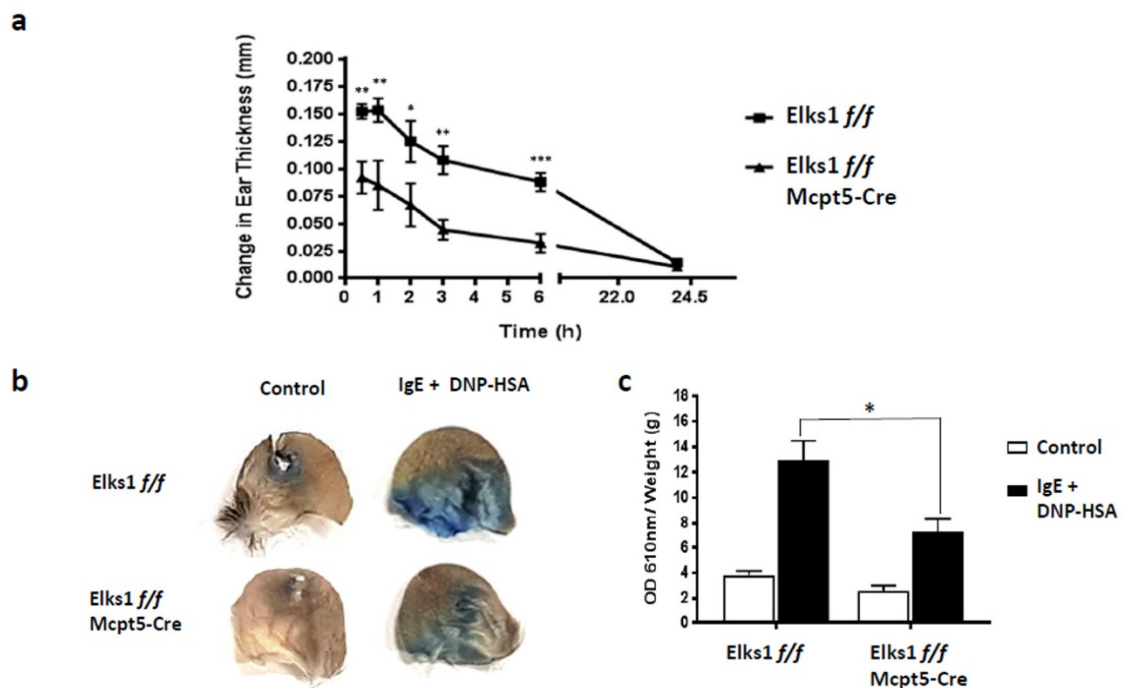


FIGURE LEGEND

- a)** *Elks1^{ff}* and *Elks1^{ff} Mcpt5-Cre* mice were injected intradermally with anti-DNP IgE (SPE-7, 100ng) in the right ear pinna, and an equal volume of HEME-Pipes vehicle in the left ear pinna. 16 hours later, DNP-HSA (200µg in 100 µL) was injected intravenously and the increase in ear thickness was recorded at intervals between 0 and 24 hours later. (n=6, *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$)
- b)** Evans blue dye extravasation from ear of *Elks1^{ff}* and *Elks1^{ff} Mcpt5-Cre* mice 30minutes after intravenous DNP-HSA (containing 1% Evans blue) administration intravenously. Picture showing ear pinnae of *Elks1^{ff}* and *Elks1^{ff} Mcpt5-Cre* mice.
- c)** Evans blue dye extravasation from panel **b** was quantified by O.D. 610nm /weight. (n=3, * $p<0.05$)