

TSLP mediates bidirectional interactions between human lung macrophages and mast cells

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June 25, 2023

Abstract

Background Thymic stromal lymphopoietin (TSLP), a pleiotropic cytokine mainly expressed by epithelial cells, plays a key role in asthma pathobiology. In humans, TSLP exists in two variants: the long form TSLP (lTSLP) and a shorter TSLP isoform (sTSLP), overlapping the lTSLP C-terminus. Macrophages (HLMs) and mast cells (HLMCs) are in close proximity in the human lung and play central roles in different asthma phenotypes. **Methods** Immunofluorescence and Western blot were employed to localize intracellular TSLP. Limited proteolysis and mass spectrometry allowed the identification of cleavage sites of TSLP caused by tryptase and chymase. ELISA assays were employed to measure TSLP and VEGF-A. **Results** TSLP was detected in highly purified ([?] 99%) macrophages isolated from human lung and subcellularly localized in the cytoplasm by confocal microscopy and Western blot. IL-4 and lipopolysaccharide induced the release of TSLP from HLMs. HLMCs contain and release tryptase and chymase that specifically cleaved TSLP. Mass spectrometric analyses of TSLP treated with tryptase showed the production of 1-97 and 98-132 fragments. Chymase treatment of TSLP generated two peptides 1-36 and 37-132. HLM activation by lTSLP induced VEGF-A, the most potent angiogenic factor, release. The four TSLP fragments generated by tryptase and chymase failed to activate HLMs. sTSLP neither activated HLMs nor interfered with activating property of lTSLP on HLMs. **Conclusions** Given the close proximity between mast cells and macrophages in the human lung, our results illuminate a new circuit between HLMs and mast cells. These findings have potential relevance in understanding novel aspects of asthma pathobiology.

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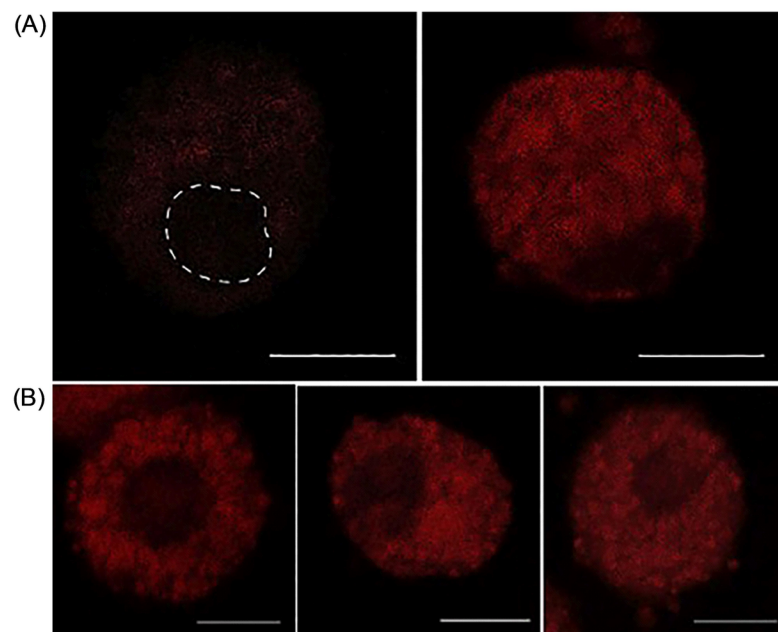


Figure1_Canè et al.

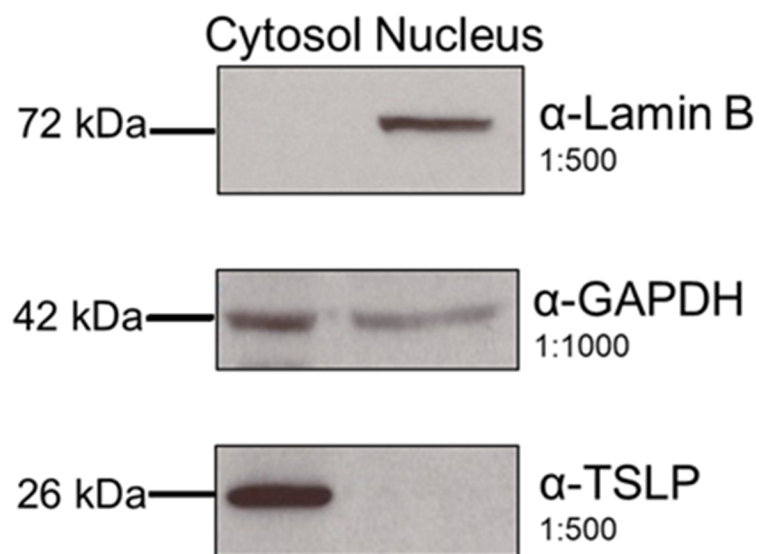


Figure 2_Canè et al.

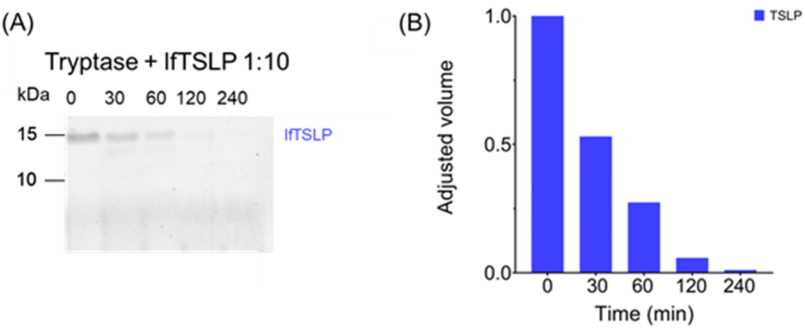


Figure 3_Canè et al.

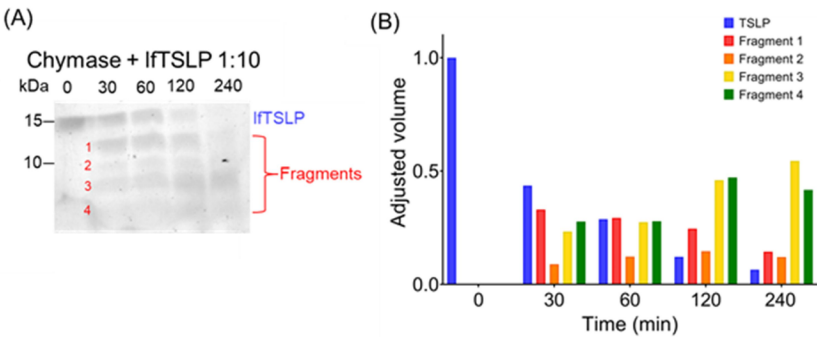


Figure 4_Canè et al.

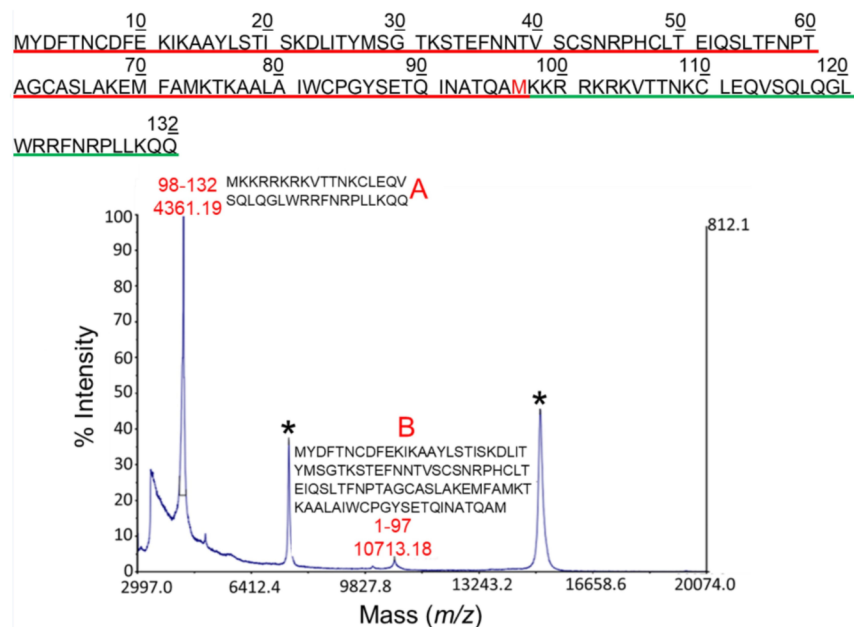


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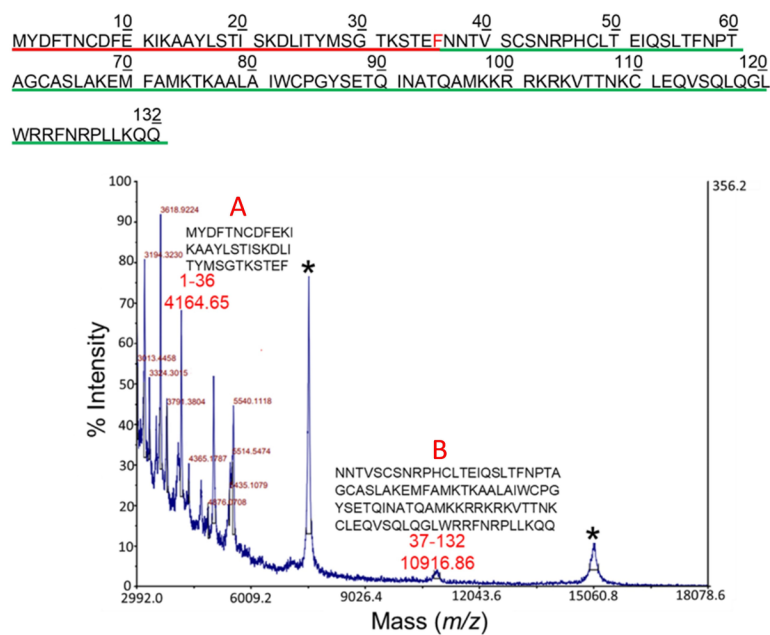


Figure 6_Canè et al.

10 20 30 40 50 60
MYDFTNCDFE KIKAAYLSTI SKDLITYMSG TKSTENNNTV SCSNRPHCLT EIQLSTFNPT
70 80 90 100 110 120
AGCASLAKEM FAMKTKAALA IWCPGYSETQ INATQAMKKR RKRKVTTNKC LEQVSQLQGL
132
WRRFNRPLLKQQ

