

# Abstract

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## Apical localization of zinc transporter ZnT4 in human airway epithelial cells and its loss in a murine model of allergic airway inflammation.

Murgia C, Grosser D, Truong-Tran AQ, Roscioli E, Michalczyk A, Ackland ML, Stoltenberg M, Danscher G, Lang C, Knight D, Perozzi G, Ruffin RE, Zalewski P.

INRAN-National Research Institute on Food & Nutrition, Roma 00178, Italy.

**BACKGROUND:** The apical cytoplasm of airway epithelium (AE) contains abundant labile zinc (Zn) ions that are involved in the protection of AE from oxidants and inhaled noxious substances. A major question is how dietary Zn traffics to this compartment.

**FINDINGS:** In rat airways, in vivo selenite autometallographic (Se-AMG)-electron microscopy revealed labile Zn-selenium nanocrystals in structures resembling secretory vesicles in the apical cytoplasm. This observation was consistent with the starry-sky Zinquin fluorescence staining of labile Zn ions confined to the same region. The vesicular Zn transporter ZnT4 was likewise prominent in both the apical and basal parts of the epithelium both in rodent and human AE, although the apical pools were more obvious. Expression of ZnT4 mRNA was unaffected by changes in the extracellular Zn concentration. However, levels increased 3-fold during growth of cells in air liquid interface cultures and decreased sharply in the presence of retinoic acid. When comparing nasal versus bronchial human AE cells, there were significant positive correlations between levels of ZnT4 from the same subject, suggesting that nasal brushings may allow monitoring of airway Zn transporter expression. Finally, there were marked losses of both basally-located ZnT4 protein and labile Zn in the bronchial epithelium of mice with allergic airway inflammation.

**CONCLUSIONS:** This study is the first to describe co-localization of zinc vesicles with the specific zinc transporter ZnT4 in airway epithelium and loss of ZnT4 protein in inflamed airways. Direct evidence that ZnT4 regulates Zn levels in the epithelium still needs to be provided. We speculate that ZnT4 is an important regulator of zinc ion accumulation in secretory apical vesicles and that the loss of labile Zn and ZnT4 in airway inflammation contributes to AE vulnerability in diseases such as asthma.

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