A possible role for TRPV4 receptors in asthma

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THE REPORT from Jia et al., the current article in focus (Ref. 15, see p. L272 in this issue), describes their findings in human bronchial smooth muscle cells in culture that can be stimulated with hypotonic solutions (15). This is an important finding with practical relevance for the understanding of the pathophysiology of bronchial hyperreactivity such as occurs in asthma. Asthma affects the populations of the United States and Europe (10, 22) and can become, in some patients, at times severe or even life threatening. Bronchial hyperresponsiveness is a hallmark of asthma. Asthma is accompanied by a denudation of the epithelial lining of the bronchi and bronchioli. This occurs within a pathophysiological framework described as “airway remodeling” (10, 22). In this condition, bronchial smooth muscles as well as nerve endings can thus become exposed directly to bronchial fluid that is itself hypotonic (see Fig. 1).

The Jia et al. paper provides evidence that one member of the transient receptor potential (TRP) vanilloid subfamily (TRPV) family of the TRP channel superfamily of ion channels (8, 14), TRPV4 (26), that is found on airway smooth muscle cells, might function in the transduction of osmolarity/hypotonicity stimuli in airways.

The TRPV receptor subfamily consists of cation-selective, calcium-permeable ion channels that are widely expressed in both excitable and nonexcitable cells. Members of this family can be activated by diverse stimuli, including chemical irritants, protons, lipids, changes in cell volume possibly via membrane deformation, mechanical stimuli, and warm/noxious heat (1, 2, 4, 5, 14, 21, 25, 26). Despite recent progress, relatively little is understood regarding how members of the TRPV subfamily might respond to these stimuli in vivo.

Hypotonicity-activated ion channels permeable to calcium are ideal candidates to lead to contraction of bronchial smooth muscle cells. Of the TRPV subfamily of the TRP channel superfamily, TRPV4 [previously named VR-OAC, OTRPC4, TRP12, or VRL-2 (9, 18, 29, 32)] has been found by several groups to show activation in response to hypotonic stimulation in heterologous expression systems (18, 29, 32). We view the Jia et al. (15) paper as an important first step in elucidating the role of TRPV receptors in asthma. However, it is likely that it is part of a very complex story. To this point, the activation by hypotonicity and mechanical stimuli has been described recently for TRPV2 also (24) [previously named VRL-1 or GRC (6, 16)]. Because Jia et al. also detected the TRPV2 transcript in the bronchial smooth muscle cell line, its possible role also needs to be addressed. In this regard, in a recent study by Muraki et al. (24), vascular smooth muscle cells were found to express both TRPV4 and TRPV2, and their response to hypotonicity became greatly diminished after transfection with a TRPV2-specific antisense, which led to a reduction of TRPV2 protein expression. The investigations of Muraki et al. and Jia et al., when taken together, imply that we need to know about the expression of both TRPV2 and TRPV4 in smooth muscle cells in both bronchial airways and in vessels and other possible locations where smooth muscle surrounds a lumen. At the mRNA level, gene expression studies can be conducted at the transcriptome level in many species, and consequently, knowledge of the comprehensive expression profiles of TRP ion channels should be addressed in future studies.

Although the “pharmacological” approach using 4α-phorbol 12,13-didecanoate and ruthenium red aids in the identification of the receptors involved with airway hyperresponsiveness, the molecular approach of achieving a specifically targeted down-regulation of protein expression would yield less ambiguous results. This is because one transcript of a given trpv gene might respond to a certain ligand/activator, yet another one will not. On the other hand, a ligand/activator may stimulate two different channels derived from different genes. The former has been demonstrated for TRPV1 (7, 27) and the latter for anandamide and TRPV1/ TRPV4 (28, 31, 34). In this context, a general question to be addressed is whether smooth muscle cells that line the lumina of various organs and that are endowed with responsiveness to osmotic stimuli (hypotonicity) and mechanical dilation are dependent on the same or a different molecular machinery to transduce the respective stimuli.

The physiological function of TRPV4 in (bronchial) smooth muscle cells in vivo can be approached by the use of trpv4+/− mice (19, 23, 30). These mice have been found to harbor abnormalities in their response to systemic osmotic and somatosensory mechanical stimuli. They have been investigated for their response to systemic osmotic stress and to external somatosensory stimuli. Thus lung function and smooth muscle cell function await exploration in these animals. In general, working with a general null genotype that is not lethal entails the possibility that other compensatory genes or pathways are upregulated in the null. This might be the case in trpv4−/− mice that show a relatively mild phenotype. To address more specifically the question of what TRPV4 does in live animals, tissue/cell-specific knockdowns will have to be generated. A smooth muscle/cell-specific cre− mouse has recently been reported by Xin et al. (33). In depth studies of gene-expression patterns (e.g., by gene arrays) can possibly lead to the isolation of bronchial smooth muscle cell-specific genes, which in turn will permit the generation of more specific cre mice. Transgenic expression of cre in mice can be accomplished not only under the control of tissue/cell-specific promoters, but also...
under the control of an inducible element, thus allowing
expression to be associated with “airway remodeling.” The bronchial epithelium is
changed from a regular single layer of bronchial epithelial cells with the
occasional goblet cell, a mucin-producing cell, to a denuded layer with gaps,
goblet cell hyperplasia, and rarefied bronchial epithelial cells, which have a
tendency to transdifferentiate to squamous epithelial cells. The underlying
basement membrane is thickened, and there is proliferation of myofibroblast
toids between the basement membrane and the smooth muscle cells, which
are hypertrophic and hyperplastic. A denuded, remodeled epithelial layer, as in
chronic asthma or other chronic conditions associated with bronchial hyper-
reactivity, would represent a pathological entryway for activators of TRPV4
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REFERENCES
1. Agopyan N, Hhati T, Yu S, and Simon SA. Vanilloid receptor activation
by 2- and 10-microm particles induces responses leading to apoptosis in

2. Agopyan N, Head J, Yu S, and Simon SA. TRPV1 receptors mediate
3. Alessandri-Haber N, Yeh J, Boyd AE, Parada CA, Chen X, Reichling
DB, and Levine JD. Hypotonicity induces TRPV4-mediated nociception
4. Caterina MJ and Julius D. Sense and specificity: a molecular identity for

5. Caterina MJ and Julius D. The vanilloid receptor: a molecular gateway
6. Caterina MJ, Rosen TA, Tominaga M, Brake AJ, and Julius D. A
capsaicin-receptor homologue with a high threshold for noxious heat.
7. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD,
and Julius D. The capsaicin receptor: a heat-activated ion channel in
8. Clapham DE, Runnels LW, and Strubing C. The TRP ion channel
see CG, Costigan M, Anand P, Woolf CJ, Crowther D, Sanseau P, and
Tate SN. Identification and characterization of a novel human vanilloid
Molecular and functional characterization of the melanin-related cation
13. Grill MA, Bales MA, Fought AN, Rosburg KC, Munger SJ, and Antin
PB. Tetrazycline-inducible system for regulation of skeletal muscle-
14. Grinnell BW and Friedman JM. Abnormal osmotic regulation in
Egan RW, and Hey JA. Functional TRPV4 channels are expressed in
Translocation of a calcium-permeable cation channel induced by insulin-
osmotically activated channel (VR-OAC), a candidate vertebrate osmore-
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Fig. 1. Airway remodeling in asthma and a potential role for transient receptor
potential vanilloid (TRPV4) on bronchial smooth muscle cells. Depicted is a
schematic drawing of a bronchial epithelium in chronic asthma, a condition
known to be associated with “airway remodeling.” The bronchial epithelium is
changed from a regular single layer of bronchial epithelial cells with the
occasional goblet cell, a mucin-producing cell, to a denuded layer with gaps,
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