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 superfamiliy 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 superfamiliy, 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. The approach by Muraki et al. to “knock down” protein expression of TRPV2 with an antisense strategy addresses the important issue of whether TRPV2 is necessary for the observed Ca2+ entry into the endothelial smooth muscle cells. Finally, it is important to elucidate the possible formation of TRPV2/ TRPV4 multiprotein complexes in smooth muscle cells.

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 downregulation 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 different molecular machinery to transduce the respective stimulus.

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

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under the control of an inducible element, thus allowing temporal control (12). In principle, this permits the specific knock down of gene function in a specific organ/cell type in a live animal at a specific time point in the life of the animal. Given the physiological and clinical relevance of contraction of smooth muscle cells in vascular beds and bronchial airways, this appears to be a worthy long-term goal.

These considerations, in principle, also apply to the TRP melastatin (TRPM3) subfamily, which has been reported to be responsive to hypotonic stimuli when expressed in heterologous cellular systems, albeit with a slightly different response profile than TRPV4 and TRPV2 (most important being a more sluggish response kinetics) (13).

The biological role of TRPV4 in the lung is likely to be more complex than its role in bronchial smooth muscle. TRPV4 gene expression has been detected in tracheal epithelial cells, bronchial glandulae, and alveolar cells, particularly macrophages (gene expression was detected by either in situ hybridization or immunohistochemistry) (Ref. 9 and Liedtke, unpublished observations). If TRPV4 is present in sensory nerve endings in lung tissue, its activation could produce bronchoconstriction through an axon reflex.

In aggregate, the paper by Jia et al. (15) points toward the key relevance that an increased understanding of bronchial smooth muscle cell contractility will have for a rational targeting of new candidate drugs aiming at bronchial hyperresponsiveness. The osmotically/mechanically activated TRPV4 channel, which might function as a transduction channel for osmotic and mechanical stimuli (3, 11, 19, 20, 25), is now a tentative new participant in this scenario. If confirmed, TRPV4 and possibly other TRP(V) channels will be targets for drug development for the treatment of bronchial hyperresponsiveness/asthma and maybe steroid-refractory asthma in particular. But we are all aware that asthma involves a diverse crowd of players, some of them from immunology, some of them from basic cell biology, and some, TRPV ion channels!

REFERENCES


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