

TRPV4 Channels: Potential Targets to Reduce the Incidence of Bronchopulmonary Dysplasia (BPD)?

Tanbir Najrana, Juan Sanchez-Esteban*

Department of Pediatrics. Alpert Medical School of Brown University. Women & Infants Hospital of Rhode Island. 101 Dudley Street. Providence, RI 02905. USA

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*Corresponding author: Juan Sanchez-Esteban, Department of Pediatrics. Alpert Medical School of Brown University, Women & Infants Hospital of Rhode Island, 101 Dudley Street. Providence, RI 02905, US Tel: 401-274-1122 ext 47483; Fax: 401-4537571; E-mail: jsanchezesteban@wihri.org

Mechanical forces generated in utero by repetitive breathing movements and by fluid distension are essential to mammalian lung development [1-3]. Paradoxically, many premature infants born with under developed lungs are exposed to excessive, non-physiological levels of stretch. This may result in ventilator-induced lung injury, which plays an important role in the pathogenesis of bronchopulmonary dysplasia (BPD), a chronic inflammatory lung disease with serious short- and long-term morbidities [4].

TRPV4 is a Ca^{2+} -permeable cation channel known to play an important role in osmotic and mechanical sensing [5]. In the adult lung, TRPV4 channels control epithelial and endothelial barrier integrity in response to stretch or increased vascular pressure and are a major determinant of ventilator-induced acute lung injury [6, 7]. However, the role of TRPV4 in injury of under developed lungs is unknown.

Premature infants born during the canalicular stage of lung development have their distal lung epithelium still covered by undifferentiated cells [8, 9]. Furthermore, these premature lungs are exposed to injury secondary to mechanical ventilation, causing pulmonary edema and inflammation. TRPV4 is expressed in adult lung [10, 11, 12]; however, whether undifferentiated distal epithelial cells express TRPV4 and the response to mechanical injury were unknown. Recent studies from our laboratory have found that TRPV4 is expressed in the fetal lung, and specifically in the bronchial and distal epithelium [13]. Moreover, in vitro experiments in isolated distal epithelial cells found that TRPV4 expression level responded to mechanical signals. This response was gestational-age dependent, being the canalicular stage of lung development the period of gestation more sensitive to mechanical injury [13].

In addition to regulating the integrity of the lung alveolar capillary endothelium [14, 15] and maintaining the airway epithelial barrier function [16], TRPV4 has been recently implied as a key mediator of inflammation. TRPV4 inhibitors have potent anti-inflammatory effects by limiting neutrophil and macrophage infiltration, and by blunting pro-inflammatory cytokine and chemokine production [17]. However, the mechanisms underlying these effects are not well-understood. One possibility

is that TRPV4 inhibitors act primarily on endothelial and epithelial cells, not only preventing changes in barrier function, but also blocking other Ca^{2+} dependent processes, such as the release of cytokines and adhesion molecules or the facilitation of neutrophil transit [18]. Studies from our laboratory found that TRPV4 regulates release of the pro-Inflammatory cytokine IL-6 in fetal epithelial cells exposed to injurious stretch [13]. Therefore, these investigations provide novel observations that distal fetal epithelial cells are an important source of Inflammatory cytokines, as previously shown in differentiated alveolar type II epithelial cells [19]. Moreover, their release, at least for IL-6, is modulated by TRPV4. All together, these studies suggest that TRPV4 may play a key role in modulating inflammation in the distal epithelium of premature lungs exposed to mechanical injury.

In summary, these data provide the first evidence that TRPV4 channels are present in the epithelium of the fetal lung and could play important role in modulating inflammation. Although TRPV4 inhibitors could be a promising therapeutic strategy for the treatment of BPD in premature infants, more studies are necessary to carefully evaluate the potential side effects related to their contribution to calcium signaling in normal fetal lung development. Specifically, genetically modified mice in the context of lung injury mediated by neonatal mechanical ventilation or hyperoxia could be effective in vivo models to further investigate the role of TRPV4 in mediating inflammation of premature lungs.

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