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Differential Organization of Airway Smooth Muscle Cells on Tubular Surface as A Novel Mechanobiology Mechanism of Airway Tissue Morphogenesis

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Abstract: Airway smooth muscle cells (ASMCs) exists within the bronchial airway wall in a form of spirally winding bundles [1]. This pattern emerges early during embryonic development and is involved in airway branching [2], providing the airway appropriate contractile capacity and resistance to circumferential tension in health or causing excessive airway narrowing in disease such as asthma. Despite its importance, the cause of ASMCs self-organization remains largely a mystery. Previously, we have demonstrated in 2D that ASMCs can sense the curvature in their microenvironment and change behaviors in differentiation, orientation and migration accordingly [3]. Here we further explore in 3D microenvironment how ASMCs collectively behave on tubular surface of substrate, which more closely mimics the confined curved space of small diameter airways. Using time lapse live cell microscopic video imaging and fluorescence confocal microscopy, we observed, to our surprise, two distinct behaviors of self-organization of ASMCs, depending whether on the concave (inner) or convex (outer) side of the tubular substrate. On concave side, cells always adapted to the curved surface into aligned arrangement perpendicular to the longitudinal axis of the tubular substrate. On convex side, the cells eventually aligned with an angle relative to the longitudinal axis, and the angle was dependent on the tubular curvature. Interestingly, this seems to be a unique phenomenon associated with ASMCs, as other cell types showed no such behaviors. Furthermore, this phenomenon appeared to be either promoted or impaired if the ASMCs were either modulated towards a more contractile phenotype or pharmacologically relaxed. The self-organization also occurred with distinct cytoskeleton remodeling, suggesting the origin of its driving force. Thus, it reveals a novel mechanobiology mechanism for airway tissue morphogenesis/regulation, which may be important for better understanding airway pathophysiology but also useful in development of new technique for airway disease treatment such as tissue regeneration.

Keywords: Airway smooth muscle cells; self-organization; concave; convex; curvature; contractile phenotype

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