Last Word on Point: Alterations in airway smooth muscle phenotype do cause airway hyperresponsiveness in asthma

Susan J. Gunst1 and Reynold A. Panettieri, Jr.2

1Indiana University School of Medicine, Department of Cell and Integrated Physiology, Indianapolis, Indiana; and 2University of Pennsylvania Perelman School of Medicine, Department of Medicine, Pulmonary, Allergy and Critical Care Division, Airways Biology Initiative, Philadelphia, Pennsylvania

TO THE EDITOR: We greatly appreciate the readers’ interest and response (see Ref. 2) to the Point:Counterpoint (4, 9) article. We wish to respond to comments focused on whether nature vs. nurture modulates the airway smooth muscle (ASM) phenotype that manifests as airway hyperresponsiveness (AHR). The nature vs. nurture argument was not our main point, rather it was the issue of whether ASM is phenotypically different in asthmatics and whether the phenotypic differences in ASM make it more contractile than non-asthmatic ASM. The question of whether the phenotypic differences in ASM arise from intrinsic genetic differences or as the result of genetic modulation due to environmental influences (either before or after birth) is not relevant to this issue if the outcome in either case is that the muscle is hyperresponsive. As we noted in our article, there is compelling data that suggest ASM in asthma is physiologically different from ASM derived from non-asthmatic subjects. This is true for animal models of asthma as well as for cells from human asthmatics, both of which have been shown to be hyperresponsive in vitro. The gene-environment interaction can induce a sustained AHR phenotype, which persists even in in vitro and ex vivo models (1, 5, 8). Importantly, substantial evidence also shows that airway inflammation can be uncoupled from AHR and suggests structural cells (epithelium, ASM, vascular smooth muscle) may evoke an AHR phenotype (3, 5–8). Unless, we use scientific approaches that incorporate integrated human cells, tissue, and in vivo platforms, our ability to identify the molecular mechanisms promoting AHR may be compromised.

DISCLOSURES
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Address for reprint requests and other correspondence: S. J. Gunst, Indiana Univ. School of Medicine, Dept. of Cell and Integrated Physiology, Indianapolis, IN (e-mail: sgunst@iupui.edu).