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Title: Substrate stiffness and geometry differentially regulate proliferation in airway smooth muscle cells

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Body: Airway smooth muscle (ASM) hyperplasia is a hallmark of asthma, attributed to excessive pro-inflammatory cytokine release. However in other cell types mechanical factors including substrate stiffness and geometry modify proliferation, and we have shown stiff substrates and 3D environments enhance ASM contractility. This may be important considering the structural changes associated with asthmatic airway remodeling. We used collagen-I coated glass, plastic and polyacrylamide hydrogels with elastic moduli ranging from 300 Pa to 19200 Pa to study mechanical regulation of hASM proliferation. Engineered microtissues consisting of ASM embedded within a collagen-I matrix were used as 3D substrates. Proliferation was assessed by BrdU or EdU incorporation in high (2-5%) and low (0.5-1%) serum. ASM proliferation in high serum was 39% lower on 300 Pa than 1200 Pa substrates, with no further increase on stiffer hydrogels or glass. Decreasing serum reduced proliferation significantly, but a different pattern was observed on each substrate; proliferation remained lowest on 300 Pa substrates, peaked at 4800 Pa and dropped on 19200 Pa and glass. In 3D cultures, proliferation in high serum was 55-60% lower than on 4800 Pa and plastic substrates. However, in low serum, 3D cultures were similar to cells grown on plastic, whereas proliferation on 4800 Pa hydrogels was ~3-fold higher. These results indicate that ASM proliferation is differentially regulated by mechanical factors, consistent with previous ASM contractility studies. This highlights the importance of establishing physiological mechanics when studying ASM in vitro, and suggests that mechanical factors may contribute to asthma pathogenesis.