Better understanding asthma by understanding smooth muscle cells

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Biomedical engineering – the science of applying high-tech engineering tools to aid and understand the human medical condition – is one of the fastest growing fields in the world. Dr. Geoff Maksym and his laboratory team at Dalhousie University are involved in leading-edge biomedical research into asthma, from the cell to the patient.

The incidence of asthma has more than doubled in the past 20 years, currently reaching epidemic proportions in developed countries. In Canada, asthma affects two million people, is the leading cause of hospitalization for children under 12, and kills 20 children and 500 adults annually. While the causes of asthma are poorly understood, Dr. Maksym's innovative biomedical research is increasing our knowledge of the disease and may ultimately lead to more effective treatments.

His work has led to a better understanding of how mechanical forces in the lung affect a person's ability to breathe. Specifically, he and his team are examining the role of physical forces on airway narrowing in asthma by investigating smooth muscles surrounding the airway. Airway smooth muscle (ASM) cells stretch during breathing and normal breathing patterns constantly put force on these muscles. As you breathe, the airway dilates, extends and retracts as the lungs inflate and deflate. In most people stretching the smooth muscle cells aids in breathing, but in asthmatics the muscle becomes too tight or too stiff to stretch effectively. This may explain why, in some cases, asthma worsens over time.

"In patients with worsening asthma," says Dr. Maksym, "it's possible ASM cells get stiffer with each attack. The stiffer cells mean the muscles have to pull harder to dilate the airways so air can get through. This compounds with each attack, so the next may be more severe. It's a catch-22 situation – the harder you breathe, the stiffer the cells become, and the stiffer the ASM cells, the harder you have to breathe. It's a gradual process that can lead to airway remodelling and stiffening of the cells.

"It's important to know how ASM cells work in order to better understand asthma," he adds. "We're examining how ASM cells change – biologically, structurally and functionally – when stimulated mechanically and in response to a contraction stimulus; for it's the contractile event that makes asthma a deadly disease."

To investigate ASM cells, his Dalhousie lab is using unique equipment – an optical magnetic twisting cytometer, one of only four in the world. Dr. Maksym helped to develop the instrument while at the Harvard School of Public Health. This and other tools measure forces and cell motion and contraction in minuscule measurements – on the nanometre scale. Tiny mag-

netic iron beads are attached to ASM cells in a culture and manipulated electromagnetically, delivering controlled mechanical stress to the cells. The resulting changes can be visually observed and measured.

His research has revealed that mechanical stress causes rapid stiffening of ASM cells and that the increase in stiffness is due to remodelling of the cytoskeleton or the cellular scaffolding within the cell itself. The results indicate that short-term mechanical stress is an important factor that may lead to rapid stiffening of ASM cells. This may be responsible for impairment of airway dilation following airway constriction in asthma. Long-duration mechanical stress leads to both stiffer cells and improved contractility, possibly leading to worsening both airway constriction and airway dilation in asthma. The findings suggest that strategies that reduce mechanical stresses in the lung such as long-term, low-dose bronchodilators may lead to less stiffening and decrease contractility in airways; but further research needs to be done to test this theory. Various questions remain to be answered: for example, how stiff are the airways of stable asthmatics compared to normal airways?; are ASMs more active in asthmatics?; do low-dose bronchodilators in culture decrease ASM stiffening, and if so do they do the same in asthmatics?

Understanding the underlying causes of asthma will lead to the development of new treatments and an improved quality of life for people with asthma.

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Research Results