PRESS RELEASE
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Researchers have identified proteins that control mucous production and suggest clues to treating colon and airway diseases

New research reveals how healthy cells in our bodies produce mucins – the main component of mucous, which protects our intestine and airway from pathogens, toxins and allergens. Scientists have already linked defects in mucins secretion to airway and colonic diseases, such as asthma or ulcerative colitis. These new processes discovered by the scientists at the Centre for Genomic Regulation (CRG) in Barcelona in collaboration with researchers at the Pompeu Fabra University, reveal how cells control quantities of mucin released and could become a new avenue to treat several mucin-related diseases.

Cells produce mucins at a constant rate, and when exposed to an allergen or pathogen, they produce more mucin in a rapid burst. Both the constant and rapid mucin secretion is controlled by calcium. CRG researchers Gerard Cantero-Recasens and Vivek Malhotra wanted to understand how normal cells secrete mucins in the right quantity and quality, so they can design procedures to correct mucin secretion defects in diseases where either too much or too little mucin is produced, such as asthma, chronic obstructive pulmonary disease, Crohn's disease and colorectal cancer.

Their data published in the journals *eLife* and *Journal of Biological Chemistry*, reveal two proteins called TRPM4 and NCX that work together to control mucin secretion both in healthy cells, and in cells derived from patients with cystic fibrosis. They have also identified a third protein called KChIP3 that senses calcium levels within healthy cells to release mucins, which is crucial to maintain the correct thickness of the mucous layer in the colon. This means cells possess means to control how much mucin they produce depending on the cellular needs. They can produce large amounts if an allergen or pathogen is present, or release it constantly to preserve the mucous layer.

"First, we carried out a genome wide screen which identified 25 proteins involved in mucin secretion in colon cancer cells," explains postdoctoral researcher Cantero-Recasens. "We discovered that a group of these proteins reside on the surface of the cells to control calcium entry, which in turn controls rapid release of mucins. The team has also discovered a calcium sensor, KChIP3, inside cells that controls baseline mucin secretion, which is crucial to maintain the correct thickness of the mucous layer. If this intracellular calcium sensor is lost, it causes massive release of mucin from colonic cancer cells."

He continues: "We were surprised by this finding - we didn't expect that cells use different sources of calcium – from internal and external sources - to control mucin secretion. We also didn't expect to find that the KChIP3 sensor controlling baseline (basal) mucin secretion does it by acting like a 'brake' to prevent mucin release. Mice without the KChIP3 gene have a much thicker mucous layer in the colon. This means KChIP3 could be a new target for drugs to control diseases with higher or lower levels of mucins."

And by studying different cell types, the team discovered the process cells use to control stimulated mucin secretion is the same in both the colon and the airways. “This is an exciting finding because it means targeting the molecules involved in mucin secretion process can be used to treat airway diseases such as asthma or chronic obstructive pulmonary disease (COPD), as well as the colon associated pathologies,” explains Dr Cantero-Recasens.

ICREA research professor at the CRG, Vivek Malhotra and his group are now working with researchers at the Hospital Del Mar and IMIM to further test whether mucins and proteins involved in mucin secretion are genetically altered in patients with diseases of the airway and colon. They are also working to find chemical means to target functions controlled by proteins in mucin secretion pathway. Together, the genetic and chemical procedures to control mucin secretion could reveal new ways to detect and control progression of asthma, chronic obstructive pulmonary disease (COPD), irritable bowel disease and colorectal cancers.

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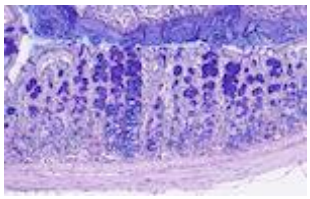
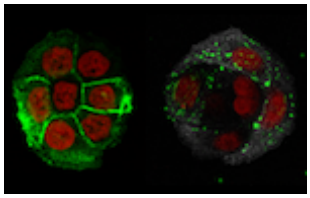
Notes to Editors:

Images available at: http://bit.ly/CRG_mucins



Colon from mice deleted of KChIP3. Section of the colon from mice deleted of KChIP3 was stained to detect mucus (in blue). Mucus producing cells are located in the colonic crypts were they secrete mucus to the lumen of the colon. Mice delete of KChIP3 show almost double amount of mucus at the lumen compared to “normal” mice. Author: Gerard Cantero -Recasens, CRG.



Colonic cells to study mucus secretion mechanism. Colonic cells are cultured in the lab and differentiated to accumulate mucus. In the image, nuclei are stained in red, in green at the left is the actin (the skeleton that holds the cells) and at the right the mucus granules. Author: Gerard Cantero -Recasens, CRG.

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Reference articles:

Cantero-Recasens, G., Butnaru, C. M., Valverde, M. A., Naranjo, J. R., Brouwers, N., and Malhotra, V. (2018) KChIP3 coupled to Ca2+ oscillations exerts a tonic brake on baseline mucin release in the colon. *Elife*. 10.7554/eLife.39729

Cantero-Recasens, G., Butnaru, C. M., Brouwers, N., Mitrovic, S., Valverde, M. A., and Malhotra, V. (2018) Sodium channel TRPM4 and sodium/calcium exchangers (NCX) cooperate in the control of Ca2+-induced mucin secretion from goblet cells. *J. Biol. Chem.* 10.1074/jbc.RA117.000848

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