Land of hope and dreams

Selection of life science literature

by Marco Confalonieri

Two recent studies opened new exciting avenues of research, respectively in the field of regenerative medicine and new treatment for airways diseases.

The first study (1) tested a method to stimulate organ tissue repair without complicated procedures. The second study (2) identified molecular pathway responsible for excess mucus production in airways suggesting new drugs that inhibit that pathway. Giacca's team at Trieste's International Centre for Genetic Engeneering and Biology (ICGEB) screened a library of human miRNAs to identify those inducing cardiomyocites proliferation. They transfected rat neonatal cardiomyocytes *in vitro* with different 200 miRNAs and measured proliferation and cell division. Fluorescence microscopy showed that rat neonatal cardiomyocytes proliferated in response to miRNA injection, and 12 days after injection, mouse neonatal hearts were enlarged, but without showing signs of cell enlargement, indicating an increased number of cells in the organ. Importantly, hearts of adult rats administered the miRNAs immediately after induced heart attack showed reduced damage and preserved function compared to the hearts of rats that didn't receive the therapy. Cardiac cells lose most of their capacity for proliferation and regeneration shortly after birth, making it difficult for hearts to recover from damage later in life. But researchers have identified four human microRNAs that can stimulate proliferation of adult rodent cardiac cells in culture and help protect against damage during heart attack *in vivo*, according to a study published in *Nature*. If the microRNAs work similarly in human cardiac cells, they may have potential as regenerative therapies after heart damage.

Holtzman et al. (2) have described the molecular pathway responsible for excess mucus in airway cells and have used that information to design a series of new drugs that inhibit that pathway. As part of the new research, the scientists discovered that a critical signaling molecule, CLCA1, has a special role in the mucus pathway. They showed that CLCA1 allows a protein known as IL-13 to turn on the major mucus gene in airway cells. The researchers also showed that CLCA1 needs help from an enzyme called MAPK13. Although there were no existing drugs that acted against MAPK13, there were several that inhibit a similar enzyme known as MAPK14, which differs slightly in structure. MAPK13 inhibitor drugs may have a possible role in related conditions with excess mucus production, like COPD, asthma, cystic fibrosis and even the common cold.

1) Functional screening identifies miRNAs inducing cardiac regeneration.

Eulalio A, Mano M, Dal Ferro M, Zentilin M, Sinagra G, Zacchina S, Giacca M

Nature doi:10.1038/nature11739

Abstract

In mammals, enlargement of the heart during embryonic development is primarily dependent on the increase in cardiomyocyte numbers. Shortly after birth, however, cardiomyocytes stop proliferating and further growth of the myocardium occurs through hypertrophic enlargement of the existing myocytes. As a consequence of the minimal renewal of cardiomyocytes during adult life, repair of cardiac damage through myocardial regeneration is very limited. Here we show that the exogenous administration of selected microRNAs (miRNAs) markedly stimulates cardiomyocyte proliferation and promotes cardiac repair. We performed a high-content microscopy, high-throughput functional screening for human miRNAs that promoted neonatal cardiomyocyte proliferation using a whole-genome miRNA library. Forty miRNAs strongly increased both DNA synthesis and cytokinesis in neonatal mouse and rat cardiomyocytes. Two of these miRNAs (hsa-miR-590 and hsa-miR-199a) were further selected for testing and were shown to promote cell cycle re-entry of adult cardiomyocytes ex vivo *and to promote cardiomyocyte proliferation in both neonatal and adult animals. After myocardial infarction in mice, these miRNAs stimulated marked cardiac regeneration and almost complete recovery of cardiac functional parameters. The miRNAs identified hold great promise for the treatment of cardiac pathologies consequent to cardiomyocyte loss.*

2) IL-13–induced airway mucus production is attenuated by MAPK13 inhibition.

Alevy YG, Patel CA, Romero AG, Patel DA, Tucker J, Roswit WT, Miller CA, Heier RF, Byers DE, Brett TJ, Holtzman MJ

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Abstract

Increased mucus production is a common cause of morbidity and mortality in inflammatory airway diseases, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. However, the precise molecular mechanisms for pathogenic mucus production are largely undetermined. Accordingly, there are no specific and effective anti-mucus therapeutics. Here, we define a signaling pathway from chloride channel calcium-activated 1 (CLCA1) to MAPK13 that is responsible for IL-13–driven mucus production in human airway epithelial cells. The same pathway was also highly activated in the lungs of humans with excess mucus production due to COPD. We further validated the pathway by using structure-based drug design to develop a series of novel MAPK13 inhibitors with nanomolar potency that effectively reduced mucus production in human airway epithelial cells. These results uncover and validate a new pathway for regulating mucus production as well as a corresponding therapeutic approach to mucus overproduction in inflammatory airway diseases.