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EurekAlert

EDITOR'S PICK
Cancer cell survival is not miR-ly dependent on p53

Squamous cell carcinoma (SCC) is a common type of skin cancer and remains one of the most resistant to available chemotherapies. Many cancer therapeutic strategies are directed at restoring the function of the tumor suppressor gene p53, because when active, cells are more sensitive to the DNA damage induced by chemotherapy. Other proteins related to p53, including p63 and p73, have also been implicated in cancer and cell sensitivity to chemotherapy. Both p63 and p73 are overexpressed in SCC, and are thought to play a role in chemoresistance. In new research, Leif Ellisen and colleagues at Mass General Hospital in Boston investigated the relationship between p63 and p73 in human and mouse SCC cells. They found that p63 negatively regulates the expression of a number of microRNAs (miRs), and that some of these miRs target p73 for inhibition. One of these, dubbed miR-193a, was also positively regulated by p73, suggesting a feedback loop that might promote chemoresistance in these cells. In a mouse model of SCC, the researchers found that inhibiting miR-193a decreased tumor growth and made the cells more sensitive to the chemotherapeutic agent cisplatin. The researchers believe that these findings identify a pro-survival mechanism in SCC, and may highlight new therapeutic targets in the fight against cancer.

TITLE: A microRNA-dependent program controls p53-independent survival and chemosensitivity in human and murine squamous cell carcinoma

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EDITOR'S PICK
Transforming skin cells into cartilage

Hyaline cartilage, composed primarily of chondrocytes in an extensive extracellular matrix, makes up the embryonic skeleton and persists in adults at the ends of bones, where it provides shock absorption and lubrication of joints. Hyaline cartilage injury often results in the formation of the scar tissue fibrocartilage or even new bone formation leading to growth impairment or osteoarthritis. However, regeneration of cartilage might be possible if researchers can develop a method to generate new chondrocytes. In this paper, Noriyuki Tsumaki and his team at the

Osaka University Graduate School of Medicine, used fibroblasts isolated from adult mouse skin, and expressed proteins that have previously been used to induce pluripotency along with a factor that promotes a chondrocyte fate. This produced cells with traits that resembled chondrocytes and produced cartilage when injected into mice. The researchers believe this may be an important step toward a therapy that will allow the repair of cartilage injury using a patient's own skin cells.

TITLE: Generation of hyaline cartilaginous tissue from mouse adult dermal fibroblast culture by defined factors

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METABOLISM
Glucose homeostasis: the collagen connection

Collagen is the major component of connective tissue, and is made up of three peptide chains (subunits) twisted together to generate fibers with strength and flexibility. Collagen V usually consists of α1(V)2α2(V) subunits, but also occurs in some tissues such as white adipose, pancreatic islets, and skeletal muscle as the poorly characterized α1(V) α2(V) α3(V) heterotrimer. In this paper, Daniel Greenspan and colleagues at the University of Wisconsin, Madison, generated mice that lacked the gene that codes for α3(V). These mice had reduced dermal fat but developed diabetes-like symptoms, exhibiting glucose intolerance, decreased numbers of pancreatic islets, hyperglycemia, and insulin resistance. The authors believe that these results show that collagen and connective tissue are critical in the proper function of cells that control metabolism, including pancreatic islets, fat cells, and skeletal muscle.

TITLE: α3(V) Collagen is critical for glucose homeostasis in mice due to effects in pancreatic islets and peripheral tissues

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ONCOLOGY
A new method for detecting cancer cells

Detecting and quantifying the cancer cells that remain after treatment or that have migrated to new malignant sites is a powerful predictor of patient survival. However, there are few diagnostic strategies that allow the identification of small numbers of these cancer cells, particularly in patients with solid tumors. In this paper, Axel Weber, Holger Christiansen and colleagues at the Children's Hospital in Lepzig, Germany, addressed this problem by taking advantage of the unique molecular signatures within the cancer cells: characteristic duplications of genomic regions called amplicons. The group used Human neuroblastoma cells with a known amplification of the MYCN locus, and developed a strategy to identify those amplicons in cancer cells within a mixed population. They have thus developed a tool that might be adapted to other cancers to specifically and sensitively detect tumor cells remnant in the bone marrow, blood, or other sites after treatment.

TITLE: Detection of human tumor cells by amplicon fusion site polymerase chain reaction (AFS-PCR)

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STEM CELLS
Turning unfertilized eggs into stem cells

It is hoped that individuals with inherited disorders such as β-thalassemia, which is caused by mutations in the beta-globin gene, might one day be cured by gene therapy and/or stem cellbased therapeutics. However, there are many obstacles preventing routine clincal use of such approaches. In this paper, John McLaughlin and his team at the Nationwide Children's Hospital in Columbus, OH have shown that they can overcome some of these hurdles and treat mice with β-thalassemia caused by dominant inheritance of disease-causing mutations. They harvested unfertilized oocytes from affected female mice and used them to generate diploid uniparental zygotes, then alloweded them to develop to the blastocyst stage and derived ES cell lines. Selection of ES cell lines lacking the disease allele provided a source of genetically corrected autologous stem cells that had not been genetically manipulated. These ES cell lines were differentiated in vitro into hematopoietic progenitor/stem cells, which were transplanted into mice with dominantly inherited β-thalassemia, leading to long-term reversion of the disease phenotype. The authors therefore suggest that their genetic correction strategy could potentially be applicable to any dominantly inherited disease. However, several obstacles to clinical use remain that are problematic for all human ES cells, including developing ways to efficiently differentiate the cells into transplantable tissue.

TITLE: Gene therapy by allele selection in a mouse model for beta-thalassemia

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HEPATOLOGY
Waste removal by the liver protects the kidney

In every tissue in the body, homeostasis requires constant breakdown of large biological molecules, and this breakdown process can generate toxic waste products. Waste can be cleared by specialized liver cells called liver sinusoidal endothelial cells (LSECs) that express receptors on their surface to specifically bind to circulating factors and mediate their endocytosis. Two of these LSEC receptors, Stabilin-1 and Stabilin-2, have been shown to bind to a number of ligands, but their exact function remains unknown.

In this paper, Cyrill Géraud and his team at the University Medical Center in Mannheim, Germany investigated the roles and functions of Stabilin 1 and 2 by genetically engineering mice that lacked these genes. Mice lacking either one of the genes were normal, but mice lacking both Stabilin 1 and 2 developed kidney dysfunction and liver fibrosis and died prematurely. These findings suggest that Stabilin 1 and 2 are required for normal clearance of one or more circulating factors and the maintenance of tissue homeostasis.

TITLE: Deficiency of liver sinusoidal scavenger receptors stabilin-1 and -2 in mice causes glomerulofibrotic nephropathy via impaired hepatic clearance of noxious blood factors

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