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Question: Are AMPA-type glutamate receptors (AMPARs) recruited to dendritic spines in the hippocampus following fear conditioning?

Background: Consolidation of long-term memories is thought to require de novo synthesis of proteins, which strengthens synapses and ultimately forges memories. AMPARs play an essential role in long-term potentiation, and GluR1, an AMPA subtype, underlies experience-dependent trafficking. Thus it was hypothesized that insertion of GluR1-containing AMPARs into the synapse could contribute to learning.

Observations: Matsuo et al. developed transgenic mice to identify the trafficking of newly synthesized GluR1 subunits following fear conditioning. They determined that GluR1 is synthesized and selectively inserted in mushroom-type spines, as opposed to thin and stubby spines, in hippocampal CA1 neurons in response to fear conditioning.

Significance: These results support the idea that, during learning, there are changes in some dendritic spines that result in a “tag” at the activated synapse, which alters trafficking of newly synthesized AMPARs to the tag, strengthening the synapse. Additionally, these data suggest that mushroom spines have greater functional relevance to learning than the other types of dendritic spines. Finally, the novel experimental approach used in these studies could prove useful in understanding the pathophysiology of the disease in humans.


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Question: Is the heme export protein, feline leukemia virus subgroup C (FeLV-C) receptor (FLVCR) necessary for red blood cell differentiation and iron homeostasis?

Background: Heme serves as a prosthetic group, which consists of an iron atom contained in the center of a large organic ring, for hemoglobin, cytochromes, and other hemoproteins. Although free heme is toxic, little is known regarding the trafficking of heme and its role in iron homeostasis. The FLVCR is a heme export protein that is hypothesized to be necessary for erythropoiesis, the process by which red blood cells are produced. These studies suggest that heme overproduction is toxic, and FLVCR was explored to determine the role of FLVCR in red blood cell differentiation and iron homeostasis.

Observations: Keel et al. generated FLVCR knockout mice and determined that they lack definitive erythropoiesis and die in midgestation. When FLVCR was deleted postnatally, it produced a total blood heme concentration deficiency. Finally, FLVCR was determined to mediate the recycling of heme from macrophages that ingest senescent red blood cells and influence the accumulation of iron in the liver, suggesting that FLVCR regulates systemic iron homeostasis.

Significance: These findings suggest that the heme export protein FLVCR is required for red blood cell differentiation and iron homeostasis. Since heme is a critical component of myoglobin, hemoglobin, cytochromes, catalases, glutathione peroxidase, hydroxylases, and nitric oxide synthase, these data may be pertinent to many physiologists. Additionally, because FLVCR mutant mice displayed abnormalities that resemble pure red cell aplasia, a type of anemia affecting the precursors to red blood cells, these results may be important for understanding the pathophysiology of the disease in humans.


Nominated by Haoyang Chen
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Question: Does the well-known tumor suppressor protein p53 regulate fertility?

Background: The protein p53 is a transcription factor that regulates the cell cycle and is therefore important for suppressing tumor formation. Although little is known regarding its normal physiological function, a few recent studies have implicated p53 as serving some function in reproduction. Therefore, in the current report, the role of p53 in regulating reproduction was determined.

Observations: Breeding mice with different p53 genotypes, Hu et al. determined that p53 was involved in maternal, but not paternal, reproduction. Specifically, they observed decreases in embryonic implantation, pregnancy rate, and litter size. p53 was found to regulate the gene encoding leukemia inhibitory factor (LIF), a cytokine highly expressed at the onset of, and essential for, the attachment and implantation of the embryo in the uterus. Further evidence of a p53-LIF interaction was found when LIF was administered to pregnant p53 knockout mice and restoration was restored by improving implantation.

Significance: These results demonstrate a novel function of p53, namely a role in regulating fertility in female mice via the regulation of LIF. Although identifying regulators of p53 as a way to suppress tumor growth has been on going for some time, they may also prove beneficial as part of fertility treatment. It will be interesting to see whether, as the authors suggest, the modulation of p53 function by certain single nucleotide polymorphisms (SNPs) in the p53 pathway affects implantation in human females and whether these SNPs are linked to cases of unexplained human infertility.
HIGHLIGHTS FROM THE LITERATURE

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Remodeling of T-tubules and reduced synchrony of Ca2+ release in myocytes from chronically ischemic myocardium


Hsc70 regulates cell surface ASIC2 expression and vascular smooth muscle cell migration.


Question: How do cardiac progenitor cells (CPCs) play in physiological aging? the role CPCs play in physiological aging may lead to ways to reverse it, ultimately extending lifespan.

Activation of cardiac progenitor cells reverses the falling heart senescent phenotype and prolongs lifespan.


Question: What role do cardiac progenitor cells (CPCs) have in cardiomyopathy associated with aging?

Background: In response to cardiac damage, CPCs can be activated by growth factors or cytokines, leading to increased cell division and repair. Interestingly, functional competent CPCs are present in the hearts of patients who have died from myocardial infarctions and in patients with end-stage ischemic cardiomyopathy. However, these functional CPCs do not repair the damage. There are several possible explanations to account for why this occurs, including that the functional CPCs may not sense there is damage or that their activation, growth, and migration may be impaired. The current study was aimed at identifying whether chronological age impacts on the number and/or properties of CPCs.

Observations: Gonzalez et al. determined that chronological aging leads to shortening of telomeres in CPCs, which leads to the generation of progeny that rapidly acquire the senescent phenotype and, ultimately, ventricular dysfunction. They found that aging of CPCs is mediated by attenuation of insulin-like growth factor-1/insulin-like growth factor receptor and hepatocyte growth factor/c-Met systems. They also found that the senescent heart contains functionally competent CPCs (with long telomeres), which, following activation, partially mitigate aging myopathy.

Significance: This report suggests aging of the heart, like other organs, results from dysfunction of stem cells. However, given that fully functional CPCs are present in the senescent heart, there is the potential to correct, at least partially, cardiac malfunctions and prolong life. Since heart failure is the leading cause of death in the elderly, understanding the role CPCs play in physiological aging may lead to ways to reverse it, ultimately extending lifespan.

Deletion of p53 as a novel anti-aging intervention 


Question: Is T-tubule density involved in the mechanism that regulates vascular smooth muscle cell (VSMC) migration?

Background: VSMCs function to regulate the luminal diameter of small arteries and veins. VSMC migration is a key event during vascular development and in response to vascular disorders. Although ion channels are thought to play an important role in regulating VSMC migration, little else is known regarding migration. Recently, a novel class of proteins, the degenerin/epithelial sodium (Na+) channel/acid sensing-ion channel (DEG/ENaC/ASIC), has been implicated in VSMC migration. Of the two groups of DEG/ENaC/ASIC proteins identified, ENaC and ASIC, ASIC is thought to play an inhibitory role in VSMC migration. This investigation explored that possibility.

Observations: Grifoni et al. determined that increasing ASIC2 expression at the surface of VSMCs inhibited their migration. In addition, because others have shown stimulated expression of ENaC and ASIC proteins are mediated by inhibition of the heat shock protein Hsc70, the authors determined that Hsc70 inhibits cell surface expression of ASIC2 and hence regulates migration.

Significance: These efforts provide evidence that Hsc70 plays an important role in regulating the trafficking of ASIC2 in VSMCs. In addition, expression of ASIC2 at the surface of VSMCs was found to inhibit the migration of these cells. This suggests that ASIC2, or its regulatory pathways, could be pharmacological targets for vascular disorders where VSMC migration is dysfunctional, such as hypertension, diabetes, and atherosclerosis.

Question: Are gap junction channels permeable to the cyclic nucleotide cAMP?

Background: Connexin (Cx) proteins assemble together to form gap junctions between the cytoplasm of two adjacent cells, allowing ions and various solutes to pass between the cells. There are over 20 Cxs identified within the human genome, but there is limited understanding of their permeability properties and their role in defining coordinated tissue function. In this report, the permeability of cAMP through gap junction channels was determined for specific connexins.

Observations: In cell lines that expressed Cx43, Cx40, or Cx26, Kanaporis et al. determined the permeability of cAMP in paired cells. One cell of the pair was transfected with the cyclic nucleotide reporter gene SpIH, and the other cell was the source of cAMP. All three connexins transferred cAMP; however, Cx40 and Cx26 exhibited reduced permeability when compared with Cx43, which were ~7-10 times more permeable to cAMP.

Significance: These results suggest that Cx43 allows cAMP to diffuse between cells in sufficient quantities to induce intracellular responses. In contrast, the reduced permeability observed in Cx26 and Cx40 may be insufficient to trigger physiologically relevant changes in a recipient cell. Elucidating the characteristics of Cxs is necessary to more fully comprehend the basal physiological state of cells in vivo, which will then allow investigations into the role(s) of Cxs in disease states.

Many proteins, interact in a manner (FIG) reactions by means of their enzyme inhibitors—enzymes that inhibit the formation of enzymes. Specialized in detoxification actions—enzymes—ener g-en, such as detoxification of small molecules by liver cells. In this manner, the liver cells maintain the physiological state of the body in vivo, which will then allow investigations into the role(s) of Cxs in disease states.