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Slc26a9 is inhibited by the R-region of CFTR via the STAS domain. Chang MH, Plata C, Sindic A, Ranatunga WK, Chen AP, Zandi-Nejad K, Chan KW, Thompson J, Mount DB, Romero MF. *J Biol Chem*. First published July 30, 2009; doi:10.1074/jbc.M109.001669.

Nominated by Walter Boron

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Question: Do the interactions between the cystic fibrous transmembrane conductance regulator (CFTR) and Slc26 proteins result in similar effects; i.e., transport activation?

Background: Maintaining ionic homeostasis is achieved by pumps (ATPases) and transporters, such as Slc26 proteins, which function as anion exchangers, channels, and sensors. In some tissues and membranes, Slc26 proteins are co-expressed with the CFTR where the STAS (sulfate transporter anti-sigma) domains of the Slc26 proteins (Slc26a3 and Slc26a6) interact in a reciprocal-stimulatory manner with the regulatory region (R-region) of the CFTR. Slc26a9 transports Cl^- and HCO_3^- through several different modalities and is also co-expressed with the CFTR, which led the authors to ask whether CFTR would affect Slc26a9 activity.

Observations: Chang et al. show that, like other members of the Slc26 protein family, the STAS domain of Slc26a9 binds to the R-region of the CFTR. However, in contrast to Slc26a3 and Slc26a6, Slc26a9-mediated ion transport is almost completely inhibited by CFTR when co-expressed in *Xenopus* oocytes. They also found that, when the STAS domain was deleted, Cl^- currents were reduced and Slc26a9 was no longer affected by CFTR. Interestingly, deletion of the STAS-domain only modestly affected the $\text{Cl}^-/\text{HCO}_3^-$ exchange activity of Slc26a9.

Significance: These findings suggest that the Slc26a9 STAS domain interacts with the CFTR R-region, which results in inhibition of ion transport. However, the STAS domain appears less critical for HCO_3^- exchange since it was unaffected by STAS deletion. Thus, although the R-region of CFTR can interact with any Slc26-STAS domain, the net physiological affect is determined by the Slc26 protein. In addition to being critical for understanding Cl^- and HCO_3^- transport in epithelial cells and impaired transport in

cystic fibrosis, these findings are also relevant for clarifying the role of Slc26 mutations associated with other human diseases.

Synapse- and stimulus-specific local translation during long-term neuronal plasticity. Wang DO, Kim SM, Zhao Y, Hwang H, Miura SK, Sossin WS, Martin KC. *Science* 324: 1536–1540, 2009.

Nominated by Michael Caplan

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Question: Does long-term potentiation involve synaptic translation of mRNA?

Background: Long-term potentiation (LTP) is a form of long-lasting synaptic plasticity caused by the simultaneous stimulation of two neurons, which results in improved communication between those neurons. LTP requires the transcription of specific genes and translation of mRNAs into proteins that need to be at the synapse where LTP took place. Since the number of synapses a neuron makes with other neurons can be in the thousands, several hypotheses have attempted to reconcile how this phenomenon is achieved. One such hypothesis suggests that this involves the translation of mRNAs that are localized to the stimulated synapses. Although there are several indirect findings that support this hypothesis, until now, no direct evidence existed.

Observations: Wang et al. used a well established model to study synaptic plasticity: the monosynaptic connection between sensory and motoneurons of the sea slug *Aplysia californica*. By fusing mRNA that encodes the sensory neuron-specific peptide neurotransmitter sensorin with a fluorescent protein, they demonstrate that mRNA translation is restricted to stimulated synapses and occurs during long-term facilitation but not during depression. They also found that both the pre- and postsynaptic neurons are necessary for local translation of mRNA. Finally, the translation of the mRNA also depended on postsynaptic changes in Ca^{2+} .

Significance: This report provides the first direct evidence that the translation of proteins does, in fact, occur at individual synapses undergoing LTP. As such, this provides solid support that local protein synthesis underlies synapse-specific forms of neuronal plasticity and will likely lead to a cascade of

additional studies aimed at elucidating the molecular basis of learning and memory.

MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice. Bonauer A, Carmona G, Iwasaki M, Mione M, Koyanagi M, Fischer A, Burchfield J, Fox H, Doebele C, Ohtani K, Chavakis E, Potente M, Tjwa M, Urbich C, Zeiher AM, Dimmeler S. *Science* 324: 1710–1713, 2009.

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Question: What is the role of microRNA (miR)-92a in angiogenesis?

Background: miRs are short, single strands of noncoding RNA that play essential roles in regulating posttranscriptional gene expression via interactions with messenger RNAs. Although a few members of the cluster of miRs (miR-17–92), which contains six miRs, are overexpressed in several cancer cells, tumors, and endothelial cells (ECs), current knowledge concerning the functions of specific miRs under normal and pathophysiological conditions is sparse. In fact, some members of the miR-17–92 cluster exhibit anti-angiogenic activity in ECs while exhibiting angiogenic activity in tumors.

Observations: Bonauer et al. determined that, in human ECs, miR-92a has a high level of expression and a role in controlling angiogenesis. They found that forced overexpression of miR-92a in these ECs resulted in a number of effects, including inhibition of sprout formation in an angiogenesis model. In a mouse model of hindlimb ischemia and myocardial infarction, they found that miR-92a expression was significantly upregulated; but when miR-92a was inhibited, angiogenesis occurred, as well as functional recovery of the damaged tissue.

Significance: These data are the first to suggest that miR-92a controls new blood vessel formation in vitro and in vivo, although, as noted by the authors, the anti-apoptotic activity of miR-92a in vivo could be mediated by an indirect mechanism. Nonetheless, miR-92a may be an attractive therapeutic target for the treatment of vascular diseases by inducing angiogenesis in endothelial cells or in cancer cells by enhancing anti-angiogenic genes.

Structure and mechanism of an amino acid antiporter. Gao X, Lu F, Zhou L, Dang S, Sun L, Li X, Wang J, Shi Y. *Science* 324: 1565–1568, 2009.

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Question: What can the crystal structure of the amino acid symporter (AdiC) elucidate about membrane transporter activity in general?

Background: Some strains of gram-negative bacteria, such as *Escherichia coli* O157:H7, are pathogens that can cause food-borne illness. To do this, these bacteria need to survive the acidic environment of the stomach. Thus they have evolved two acid-resistance systems that utilize arginine:agmatine (AdiC) and glutamate:γ-aminobutyric acid (GadC) antiporters to expel protons from the intracellular milieu. Both AdiC and GadC belong to the amino acid/polyamine/organocation (APC) superfamily of membrane transporters, and this report describes the crystal structure of AdiC.

Observations: Gao et al. describe a crystal structure of AdiC with 12 transmembrane domains that form the central cavity where substrate binding would occur. By comparing this structure to those of sodium-coupled symporters recently crystallized, all in different conformations, the authors were able to describe an alternating access model that could account for transport of solutes across transporter membranes.

Significance: Resolution of the crystal structure of AdiC helps to elucidate the mechanism that allows these enteric bacteria to survive the acidic conditions of their host. Moreover, these findings demonstrate that AdiC has a structural fold in its core that is remarkably similar to several sodium symporters, all of which are encoded by different gene families and have significant differences in their amino acid sequences compared with AdiC. Thus it is possible that all of these co-transporter families share a common ancestor.

Fluorescent False Neurotransmitters Visualize Dopamine Release From Individual Presynaptic Terminals. Gubernator NG, Zhang H, Staal RG, Mosharov EV, Pereira DB, Yue M, Balsanek V, Vadola PA, Mukherjee B, Edwards RH, Sulzer D, Sames D. *Science* 324: 1441–1444, 2009.

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Question: Is it possible to directly observe the release of neurotransmitters from synaptic vesicles of individual synapses?

Background: Communication between neurons in the central nervous system requires the release of neurotransmitter (NT) from the presynaptic terminal into the synaptic cleft. However, prior to NT being released, it must be transported into synaptic vesicles. This phenomenon is accomplished, in part, by the vesicular monoamine transporter 2 (VMAT2). Until now, synaptic vesicle membrane fusion could be observed, but the available techniques were not capable of allowing observation of NT release from the synaptic vesicles of individual synaptic terminals.

Observations: Using an ingenious approach, Gubernator et al. took advantage of the fact that VMAT2 is somewhat promiscuous, which allows for transport of other phenylethylamines, including synthetic ones (e.g., amphetamines), into presynaptic vesicles. Hence, a fluorescent false NT (FFN) was designed as a fluorescent substrate of VMAT2. The FFN was shown to accumulate in vesicles of chromaffin cells that express VMAT1 (a closely related protein), an effect that could also be inhibited. Finally, they were able to demonstrate accumulation and stimulus-dependent release of the FFN in mouse brain slices from the striatum, a brain region that is densely populated with dopamine terminals. This approach showed that the activity of individual synapses changes with the stimulation frequency, revealing a new form of synaptic plasticity.

Significance: The elegant design of these studies provides a significant methodological advance that allowed the first direct visualization of neurotransmitter release from hundreds of synapses. Although the implications for understanding the synaptic release of monoamines are substantial, the promise of applying this innovative approach to other NTs is an equally exciting prospect. The

ability to elucidate the details of monoamine release from synaptic vesicles is exciting since it has implications for understanding details of many disorders associated with dysfunctional monoamine systems, for example, schizophrenia, addiction, and depression, to name just a few.

Epithelial IgG and its relationship to the loss of F508 in the common mutant form of the cystic fibrosis transmembrane conductance regulator. Treharne KJ, Cassidy D, Goddard C, Colledge WH, Cassidy A, Mehta A. *FEBS Lett* 583: 2493–2499, 2009.

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Question: What underlies the inflammation of the respiratory epithelium associated with cystic fibrosis (CF)?

Background: CF mostly occurs (~70% of cases) because of a mutation of the CF transmembrane conductance regulator (CFTR) that results from the deletion of the 508th phenylalanine (F508) in the CFTR protein. This single deletion leads to the multi-system CF disease that has many unexplained characteristics. The most debilitating feature is uncontrolled inflammation of the respiratory epithelium arising postinfection with staphylococci and pseudomonas species. Curiously, such mucosal infection occurs without spread into the blood, which suggests an epithelial defect. F508 is in the first nucleotide binding domain (NBD1) of CFTR where it is part of an accessible loop on the top of NBD1 that may participate in protein-protein interactions. The authors propose that one such heterologous interaction underlies the dysfunctional immune response associated with CF.

Observations: Utilizing several independent methods, Treharne et al. determined that the F508 region of CFTR interacts with intra-epithelial IgG. In fact, they provide evidence that suggests this interaction can occur in vivo since IgG both colocalizes apically and co-precipitates with wild-type CFTR, and the CFTR mutation can abrogate expression and colocalization of epithelial IgG. In addition, CFTR peptide binding of IgG in vitro was found to be dependent on the presence of F508.

Significance: These findings provide new insight into how mutation of F508 could lead to inflammation of the respiratory epithelium by failing to interact with intra-epithelial IgG, which provides a direct link between normal CFTR and the adaptive immune system. Thus these data provide an association between the clinical manifestations of CF and the most common mutation of CFTR.

High frequency spinal cord stimulation of inspiratory muscles in dogs: a new method of inspiratory muscle pacing.

DiMarco AF, and Kowalski KE. *J Appl Physiol*. First published June 11, 2009; doi:10.1152/jappphysiol.00252.2009.

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Question: Can the current clinical limitations of diaphragm pacing be achieved by applying high-frequency stimulation to the spinal cord?

Background: Patients with injuries that transect high in the cervical spinal cord (C2–C3), which results in paralysis of all four limbs (tetraplegia) and respiratory failure, often require mechanical ventilation to assist with breathing. Diaphragm pacing (DP) is a procedure developed over 40 years ago to assist tetraplegic patients to breathe via low-frequency (<20 Hz) stimulation of the phrenic nerve, which thus eliminates the need for mechanical ventilation and significantly improves quality of life for some patients. However, the majority of patients still require mechanical stimulation. Inadequate inspired volumes may result from incomplete phrenic nerve activation, lack of coincident intercostal muscle activation, conversion of the diaphragm to a type I muscle with consequent reduction in maximum force generation, and the abnormal recruitment of more highly fatigable before fatigue-resistant motor units.

Observations: DiMarco and Kowalski describe a novel method of motoneuron activation that more closely replicates normal physiology. They found that when high-frequency (>200 Hz) stimulation was applied to the ventral surface of the spinal cord, high in the thoracic region, both the diaphragm and inspiratory intercostal muscles were

activated at physiological firing frequencies, resulting in the generation of large inspired volumes. Importantly, this means of ventilation could be maintained for up to 6 h without system fatigue.

Significance: Similar to normal physiological conditions, this method of stimulation activates the intercostal and diaphragm muscles in concert, resulting in inspired volume generation approaching the inspiratory capacity. Additionally, and perhaps more importantly, this technique avoids fatigue by recruiting motor units in a fashion more closely resembling physiological activation. Although these findings need to be extended over a longer period of time and evaluated in clinical trials, the potential application to patients with cervical spinal cord injuries is promising.

Aging and muscle fiber type alter K⁺ channel contributions to the myogenic response in skeletal muscle arterioles.

Kang LS, Kim S, Dominguez JM 2nd, Sindler AL, Dick GM, Muller-Delp JM. *J Appl Physiol* 107: 389–398, 2009.

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Question: Do aging and muscle type affect the role of K⁺ channels in the myogenic response of skeletal muscle arterioles?

Background: The constant stimulation of muscles in the walls of blood vessels (vasomotor tone) is regulated by the myogenic response, which refers to an autoregulatory contraction or dilation in response to changes in transmural pressure. Interestingly, as we age, the myogenic response declines—a phenomenon observed in both mesenteric and skeletal muscle arterioles, but with unknown origins. In addition, although the generation of myogenic tone depends on voltage-gated Ca²⁺ channels, the counterbalancing mechanisms of dilation are less clear, although several types of K⁺ channels have been implicated.

Observations: Kang et al. hypothesized that large conductance Ca²⁺-activated (BK_{Ca}) and voltage-dependent K⁺ (K_V) channels regulate myogenic tone and that aging and muscle fiber type would reveal changes in the relative contributions of these channels. They found that the age-associated decrease in the myogenic response was due, in part, to

the function of K_V and BK_{Ca} channels. Also, as predicted, the contribution of K_V and BK_{Ca} channels to regulation of myogenic tone varied with the type of muscle fiber.

Significance: Building on the previous reports from Muller-Delp et al., these findings suggest that K⁺ channels are indeed responsible for the opposing Ca²⁺ channel-induced contraction in skeletal muscle arterioles. Moreover, the age-induced decrease in the myogenic response is associated with changes in specific K⁺ channels. Future studies will undoubtedly be designed to determine whether the age-related decrease in vascular function is due to physical inactivity of the elderly or a primary effect of aging.

Cerebral microvascular endothelial cell Na⁺/H exchange: evidence for the presence of NHE1 and NHE2 isoforms and regulation by arginine vasopressin.

Lam TI, Wise PM, O'Donnell ME. *Am J Physiol Cell Physiol* 297: C278–C289, 2009.

NHE1 is a luminal Na⁺/H⁺ exchanger in mouse choroid plexus and is targeted to the basolateral membrane in Ncb1/Nbcn2-null mice. Damkier HH, Prasad V, Hübner CA, Praetorius J. *Am J Physiol Cell Physiol* 296: C1291–C1300, 2009.

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Question: How does the Na⁺/H⁺ exchanger NHE1 contribute to the blood-brain barrier (BBB)?

Background: Na⁺-H⁺ exchangers (NHEs) are involved in numerous physiological processes, including pH regulation, cell volume homeostasis, and ion transport across endothelia and epithelia. As such, NHEs are hypothesized to contribute to maintaining the BBB, which restricts large, hydrophilic and/or polar substances from diffusing into the cerebrospinal fluid (CSF). In fact, some evidence supports the idea that NHEs contribute to CSF secretion by the choroid plexus epithelium (CPE), which is one component of the BBB. Additional evidence comes from studies of ischemic stroke, which suggest that, after the first few hours of an ischemic stroke, NHEs contribute to

edema formation via increased Na^+ and water transport across microvascular endothelial cells, the other BBB component.

Observations: The report from Damkier et al. investigated localization and activity of NHE1 in wild-type (wt), NHE1-knockout (KO), and NCBE/NBCN2-KO mice, the latter of which is a Na^+ - HCO_3^- importer in CPE cells implicated in CSF secretion. Their findings indicate that NHE1 protein is localized to the luminal membrane domain in wt-mouse and human CPE but is translocated to the basolateral membrane in NCBE/NBCN2-KO mice. They also determined that the Na^+ -dependent pH_i recovery was abolished in the NHE1-KO mice, whereas it was increased in NCBE/NBCN2-KO mice, both relative to NHE1-wt mice. Lam et al. sought to determine which NHE protein isoform(s) are expressed in BBB endothelial cells and how ischemic factors affect their activity. They identified expression of NHE1 and NHE2 proteins in microvascular endothelial cells, predominately in the luminal BBB membrane. They also found that various ischemic factors stimulate Na^+ / H^+ exchange in brain microvascular endothelial cells.

Significance: O'Donnell and colleagues' findings further elucidate the cellular mechanisms responsible for maintaining the BBB under normal physiological conditions, as well as those that underlie the pathophysiology associated with cerebral edema formation during ischemic conditions. Praetorius and colleagues findings suggest the NHE1 may serve a compensatory role after a loss of Na^+ loader and pH_i regulatory functions, which would explain its translocation from the luminal to the basolateral membrane. Collectively, these two recent articles in *AJP Cell Physiology* emphasize important mechanisms whereby NHE is regulated in the different components of the BBB: the choroid plexus and microvascular endothelial cells, including on different membranes of these polarized cells.

Defective domain-domain interactions within the ryanodine receptor as a critical cause of diastolic Ca^{2+} leak in failing hearts. Tateishi H, Yano M, Mochizuki M, Suetomi T, Ono M, Xu X, Uchinoumi H, Okuda S, Oda T, Kobayashi S, Yamamoto T, Ikeda Y, Ohkusa T, Ikemoto N, Matsuzaki M. *Cardiovasc Res* 81: 536–545, 2009.

Nominated by Litsa Kranias
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Question: What domain interactions within the ryanodine receptor underlie the Ca^{2+} leak observed in heart failure?

Background: Heart failure is associated with a decrease in cardiac contractility that is thought to be caused by a reduction in myocyte Ca^{2+} transients. A central factor limiting Ca^{2+} transient amplitude is decreased sarcoplasmic reticulum (SR) Ca^{2+} content, which is determined by the balance between SR Ca^{2+} uptake (via SERCA) and Ca^{2+} efflux via the ryanodine receptor (RyR). Accumulating evidence suggest that a leak of Ca^{2+} through RyR2 decreases the amount of Ca^{2+} required by the SR for an efficient contraction, resulting in contractile dysfunction. Thus diastolic Ca^{2+} leak through the RyR2 is hypothesized to underlie one of the problems in failing hearts.

Observations: Building on their recent findings, which suggest that a defective interaction between the NH_2 -terminal domain and central domain of RyR2 may cause Ca^{2+} leak in failing hearts, Yano and colleagues investigated the mode of interdomain interactions among the NH_2 -terminal, central, and I-domains and their role in regulating channel activity. They determined that defective interdomain interactions between NH_2 -terminal and central domains induce diastolic Ca^{2+} leak, which leads to heart failure and arrhythmia. In contrast, the COOH-terminal region was not found to interact with the NH_2 -terminal or central domain.

Significance: This article demonstrates that the NH_2 -terminal and central domain interactions within RyR2 can affect Ca^{2+} leak from the SR and includes new information about structure-function of RyR2 and how these relationships are altered in failing cardiomyocytes. Interestingly, these domains are central to several identified mutations associated with catecholaminergic polymorphic ventricular tachycardia. As such, novel therapeutic strategies could be developed to correct the defective interdomain interaction within RyR2 to prevent heart failures associated with these defects.

Regulation of the human cardiac mitochondrial Ca^{2+} uptake by 2 different voltage-gated Ca^{2+} channels. Michels G, Khan IF, Endres-Becker J, Rottlaender D, Herzig S, Ruhparwar A, Wahlers T, Hoppe UC. *Circulation* 119: 2435–2443, 2009.

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Question: Is there direct evidence of a second mitochondrial Ca^{2+} uptake pathway beyond the Ca^{2+} uniporter (MCU) described in COS-7 cells?

Background: In non-human cells, the transport of Ca^{2+} into mitochondria is mediated by a Ca^{2+} uniporter (MCU), which can be inhibited by nanomolar concentrations of ruthenium red (RuR) or its analog. An additional RuR-insensitive uptake pathway has also been suggested. Recently, first direct measurements of MCU-mediated Ca^{2+} currents were performed in mitoplasts, which are vesicles of the inner mitochondrial membrane, from COS-7 cells (a cell line derived from non-human primates), whereas the function of the non-MCU Ca^{2+} uptake pathway thus far was only indirectly evaluated. As such, the extrapolation value of these data to human physiology has been questioned.

Observations: Michels et al. sought to directly record Ca^{2+} channels of human cardiac mitochondria. They discovered two previously unknown voltage-gated channels (mCa1 and mCa2) that selectively transport Ca^{2+} into the mitochondrial matrix of human cardiac cells. Interestingly, mCa1 was inhibited by the RuR analog at concentrations similar to the MCU, whereas mCa2 was only affected by much higher concentrations. They also demonstrated that the activity of both channels is decreased under failing heart conditions, making them less efficient at transporting Ca^{2+} .

Significance: The biophysical and pharmacological features of mCa1 suggest it is the human MCU previously described in COS-7 cells. Moreover, for the first time, a second mitochondrial Ca^{2+} channel (i.e., mCa2) has been directly recorded exhibiting properties of the non-MCU Ca^{2+} uptake pathway. Since the function of both these channels is impaired in heart failure, further elucidation of these pathways could reveal that the decrease in cardiac energy levels and flux observed in heart failure is mediated by the dysfunction of these channels and thus provide novel targets for pharmaceutical interventions.

Coupling between the voltage-sensing and phosphatase domains of Ci-VSP. Villalba-Galea CA, Miceli F, Tagliatalata M, Bezanilla F. *J Gen Physiol* 134: 5–14, 2009.

Nominated by Angus Nairn
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Question: How does coupling occur between the voltage-sensing (VSD) and phosphatase domains (PD) of the only known voltage sensor-containing phosphatase (VSP)?

Background: *Ciona intestinalis* (Ci) is a saclike filter feeder with a VSP, which is conserved in humans. The CiVSP is unique because, until its discovery, only voltage-gated ion channels were thought to be capable of regulating enzyme activity. CiVSP has a domain that closely resembles the VSD of other voltage-gated channels. This is linked to the VSP, which has a putative PD with three basic residues reminiscent of a region between the VSD and catalytic domain of the enzyme known as PTEN.

Observations: Although several studies have described the effects of amino acid deletions on CiVSP and PTEN activity, Villalba-Galea sought to determine the mechanism of coupling between the VSD and PD of CiVSP. They found that, when two arginine residues of CiVSP (R253 and R254, which are homologous to R14 and R15 in PTEN) are mutated to alanines, the activity of the phosphatase is perturbed. Subsequently, they tried to rescue the activity of the enzyme by introducing lysines, but this was unsuccessful. Finally, they observed abnormal kinetics and steady-state voltage dependence of the “sensing” charges located in the fourth transmembrane domain.

Significance: This report has two primary findings. The first is that coupling between the VSD and PD of CiVSP is an arginine-specific interaction between the PBD and the membrane. Second, interactions between R253 and R254 with the membrane are necessary to prevent the voltage sensor from moving during the catalytic action of the phosphatase. These findings provide a step toward better understanding the cellular functions of VSP and elucidating why it is the only enzyme currently known to directly couple with a VSD.

Increased InsP3Rs in the junctional sarcoplasmic reticulum augment Ca²⁺ transients and arrhythmias associated with cardiac hypertrophy. Harzheim D, Movassagh M, Foo RS, Ritter O, Tashfeen A, Conway SJ, Bootman MD, Roderick HL. *PNAS* 106: 11406–11411, 2009.

Nominated by Ole Petersen
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Question: Do inositol 1,4,5-trisphosphate receptor (InsP3R) Ca²⁺ channels have a role in the remodeling of Ca²⁺ signals associated with cardiac hypertrophy?

Background: Cardiac hypertrophy is one of two ways the heart increases in size; the other being dilation. While dilation involves an increase in the size of one or more of the heart chambers, hypertrophy refers to an increase in the thickness of the heart muscles, usually in one ventricle. Hypertrophy, which occurs in response to aerobic exercise and pathological conditions, is accompanied by remodeling of Ca²⁺ signaling. Although inositol 1,4,5-trisphosphate receptor (InsP3R) Ca²⁺ channels are not the predominant Ca²⁺ channel in cardiomyocytes, they have recently been found to have an important role in cardiac physiology, and signals arising from InsP3Rs can also act to induce cardiac hypertrophy. Thus this study was designed to understand the role of InsP3Rs in the enhanced Ca²⁺ release associated with cardiac hypertrophy.

Observations: Harzheim et al. determined that both the enhancement of Ca²⁺ fluxes and the spontaneous arrhythmogenic Ca²⁺ signals associated with hypertrophy are mediated by an increase in the expression of InsP3R channels. Interestingly, InsP3R expression was specifically increased in regions where ryanodine receptors (the main Ca²⁺ channel in cardiomyocytes) are expressed. This led to enhanced Ca²⁺ release through the ryanodine receptors, thus causing greater contraction and an increase in spontaneous openings of ryanodine receptors, which may underlie arrhythmogenic Ca²⁺ signals.

Significance: The data presented in this paper elucidate a molecular mechanism underlying Ca²⁺ channel remodeling associated with cardiac hypertrophy and the ventricular arrhythmias triggered during hypertrophy. Given that cardiovascular

disease accounts for a third of all deaths, these findings are of considerable importance for our understanding of cardiac arrhythmias, which can lead to sudden death. Thus these findings underscore the importance of InsP3Rs in cardiac pathology and may represent an important target for therapeutic intervention.

The Ca²⁺ channel TRPML3 regulates membrane trafficking and autophagy. Kim HJ, Soyombo AA, Tjon-Kon-Sang S, So I, Muallem S. *Traffic* 10: 1157–1167, 2009.

Nominated by Ole Petersen
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Question: Where is TRPML3 expressed, and what is its function?

Background: The family of transient receptor potential ion channels (TRPML) consists of loosely related proteins that are permeable to cations. TRPML3 was recently determined to function as an inward rectifying Ca²⁺ channel that is regulated by Na⁺ and extracytosolic H⁺. In addition, TRPML3 is mutated in the mouse varitint-waddler, resulting in a gain-of-function phenotype, auditory hair cell death, and deafness. However, not much else is known about the localization and cellular functions of TRPML3.

Observations: Kim et al. determined that TRPML3 is heavily glycosylated and expressed in many cellular compartments that are, in large part, segregated from TRPML1. In addition, TRPML3 was found to have a role in the regulation of endocytosis and membrane trafficking. Finally, their data suggests that TRPML3 is necessary for autophagy, the catabolic process that involves the degradation of a cell's components through the lysosomal machinery.

Significance: This paper reveals an important role of TRPML3 in the regulation of endocytosis, membrane trafficking, and autophagy. TRPML3 likely does this by controlling the Ca²⁺ concentration in the vicinity of the relevant cellular organelles. In view of the current, very strong interest in the role of autophagy in various disease processes, this is an important paper providing new mechanistic insights.