52-Subg
Signaling Reactions on the Membrane: The Roles of Force, Space, and Time
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No abstract.

53-Subg
Lamin-A is Mechanosensitive to Matrix Stiffness and Couples to the Retinoic Acid Pathway in Differentiation
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Matrix elasticity helps direct lineage specification of human bone marrow-derived MSCs in culture toward bone, fat, or other tissue types with mechanisms based in part on myosin-II generated stresses. We found with both gel systems and nano-collagen films that matrix rigidity leads to higher levels of nucleoskeletal protein lamin-A. Stem cell differentiation into fat on soft matrix was enhanced by low lamin-A levels, while differentiation into bone on stiff matrix was enhanced by high lamin-A levels. Our results show that lamin-A transcription was regulated by the vitamin A/retinoic acid (RA) pathway that plays a role in development and regeneration but lamin-A protein regulates nuclear translocation of the RA receptor gamma isoform (RARG), increasing fourfold from soft to stiff matrix and suppressed by lamin-A knockdown. We also overexpressed the membrane protein SUN2, which shuttles from the endoplasmic reticulum (ER) to the inner nuclear envelope, where it cross-links nesprins and the cytoskeleton to lamin-A (based on co-IP). SUN2 overexpression appears to saturate cross-linking sites, leading to nuclear rounding, decreased lamin-A levels, and higher RARG in the cytoplasm. Based on RA pathway effects on lamin-A expression in cells on stiff matrix, we expected antagonists to RA and specifically RARG to increase osteogenesis, and we confirm this. Moreover, the increased osteogenesis with antagonists was nullified by lamin-A knockdown, consistent with a specific role in stiff tissue differentiation.

54-Subg
Environmental Sensing by the ENVZ Mechansensor
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No abstract.

55-Subg
Nonlinear Elasticity of Muscle and Its Role in Motor Control
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Holding an object without crushing or dropping it is trivial. But, decades of research in robotics has shown otherwise. Maintaining a static grasp, i.e. postural stability of the fingers, conflicts with the demands of regulating force at the fingertips. We revisit this old problem of stable static contact with simultaneous fingertip force control, and show that the control is greatly simplified by using actuators with well-designed elastic properties. Actuators that produce force as the output, in response to a control input, are well-suited to regulate the fingertip contact force. Such force actuators, like high quality electric motors, maintain a nearly constant force output independent of any displacement imposed upon them, in effect having zero stiffness. This insensitivity of the actuator to displacements induces a postural instability of the finger.
We show that the postural instability can be alleviated if the actuators are non-ideal and possess nonlinear elastic properties, namely stiffness that is linearly proportional to the force output. Such an actuator resembles a Hill-type model for muscle, with an ideal force actuator in parallel with a spring that has an exponential force-displacement relationship. Experiments that subject deafferented skeletal muscle to small displacements have shown that the stiffness of muscle scales linearly with its force output, the exact feature that our calculation shows is necessary for postural stability. This nonlinear elastic property of muscle has its roots in the cross-bridge model of muscle function, originally proposed by A.F. Huxley. Our results are not specific to the finger or specific limb, rather they generalize to any appendage such as legs or tentacles, which have more internal degrees of freedom than imposed by the surrounding environment alone.
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56-Subg
Childhood Sweetheart vs Late Suitor: CaV Channel Regulation by Auxiliary Beta and Alpha2Delta Subunits
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High-voltage-activated calcium (CaV) channels link electrical signals to the inflow of Ca2+ ions that trigger biological responses in excitable cells. CaV channels are macromolecular complexes containing pore-forming alpha1 proteins primarily assembled with auxiliary beta and alpha2delta subunits. Both CaVbeta and alpha2delta subunits augment CaV channel currents by enhancing alpha1 trafficking to the cell surface. Whereas CaVbeta (the childhood sweetheart) associates early with alpha1 in the endoplasmic reticulum and promotes forward trafficking, alpha2delta (the late suitor) enhances CaV surface density by stabilizing mature channels at the plasma membrane. Beyond their direct regulatory effects on CaV channels, CaVbeta and alpha2delta are the physical targets for powerful channel modulation by small monomeric G-proteins (RGK) and the anti-epileptic drug, gabapentin, respectively. I will discuss our findings on the different determinants and mechanisms underlying CaV channel regulation by CaVbeta and alpha2delta subunits, and implications of the work for physiological and therapeutic modulation of CaV channels.

57-Subg
Dual Regulation of M-Type K+ Channels by AKAP79/150 Signaling Complexes
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M-type K+ channels, comprised of KCNQ2-5 (Kv7.2-7.5) subunits, play key roles in the regulation of neuronal excitability. We study the regulation of M-channel activity and transcriptional expression by A-kinase-anchoring protein (AKAP)79/150. Our FRET and functional studies suggest AKAP79/150 action correlates with thePIP2-depletion mode of neuronal INa suppression, and is disrupted by functional calmodulin. The modulation of M current involves recruitment of PKC to the channels, their subsequent phosphorylation, and likely decreased affinity for PIP2. The complex orchestrated by AKAP79/150 also includes M1 muscarinic receptors, thus constituting a “signalsome” spanning the initiating receptor to channel target. We have discovered a novel mechanism regulating KCNQ2/3 transcriptional expression by neuronal activity, involving calcineurin and Nuclear Factor of Activated T-cells (NFAT) transcription factors, orchestrated by AKAP79/150. The signal requires Ca2+ influx through L-type Ca2+ channels and both local and global Ca2+ elevations. AKAP79/150 and the complex it organizes thus mediate activity-dependent M-channel transcription, which may potentially serve throughout the nervous system to limit over-excitability associated with disease states such as epilepsy. We are now utilizing stochastic optical reconstruction microscopy (STORM) offering sub-diffraction (~20 nm) resolution, to directly visualize these AKAP79/150 signaling complexes and interactions between AKAP79/150, ion channels and receptors in neurons. STORM uses dyes that can cycle between a dark and a fluorescent state thousands of times, thus enabling detection of the precise localization of the center of these scattered spots given by cumulative integration of each cycle. Using multi-color STORM to simultaneously image AKAP150, KCNQ2-3 or KCNQ5 channels, and receptors, we observe AKAP150 to form signaling clusters with the channels and receptors at the single-complex level. We have also obtained evidence that AKAP79/150 links different channel types together, raising the possibility of their functional, as well as physical, coupling.

58-Subg
Auxiliary-Subunit Dependent Modulation of SLO1 BK Channels that Underlie the Hypotensive Effect of Fish Oil
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Long-chain omega-3 fatty acids are thought to offer many health-promoting effects but their molecular effectors are only beginning to be elucidated. SLO1 BK channel complexes are subject to modulation by select omega-3 fatty acids in an auxiliary subunit-dependent manner. In predominantly vascular Slo1+/- complexes, docosahexaenoic acid (DHA), an omega-3 fatty with a 22-carbon chain, reversibly increases ionic currents up to ~20 fold by accelerating the opening transition of the ion conduction pathway in the absence of the allosteric influences of the voltage and Ca2+.