The compounds slow recovery from inactivated states in a voltage dependent manner by stabilizing the inactivated-state of the channel. The selective compounds have significantly longer residency times than pore targeting compounds that contribute to higher potency. Finally, we have established that in adult mouse brain slices, the selective targeting of Nav1.6 and Nav1.2 inhibits action potential firing in excitatory neurons, but not in inhibitory interneurons, providing a unique approach for treatment of epilepsy that selectively down regulates excitatory and spares inhibitory networks.

2446-Plat

Comparative Study of the Effects of an *SCN5A* Mutation within a Family Diagnosed with Brugada Syndrome using iPS-CM

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Brugada Syndrome (BrS) is a cardiac arrhythmogenic disease that predisposes to sudden cardiac death. It is associated with mutations in the *SCN5A* gene, encoding the cardiac sodium channel alpha subunit ($Na_V1.5$). We investigated a mutation in the *SCN5A* gene (c. 4573 G>A; $Na_V1.5$_p.V1525M), associated to BrS. Our objective was to analyze the differences in the sodium current (I_{Na}) properties among induced pluripotent stem cell-derived cardiomyocytes (iPS-CM) from three members of a family with two heterozygous carriers and one non-carrier of the mutation. Dermal fibroblasts from the three family members were reprogrammed to iPSc and further differentiated to beating iPS-CM monolayers. I_{Na} was studied using the whole-cell patch clamp technique. A total loss of I_{Na} was observed in a high percentage of the cells recorded from both mutation carriers (62% n=53 and 54% n=37, respectively). In the remaining cells, with measurable I_{Na}, we observed a 77.3% (n=19) and an 82% (n=13) reduction in I_{Na} density, compared to the non-carrier individual (n=13). Recovery from inactivation time constant was increased only in one of the two mutation carriers. We confirmed that *SCN5A* expression was comparable in the three family members' iPS-CM by qPCR. In addition, we studied the mutation in tsA201 cells transfected to heterozygously express mutation ($Na_V1.5^{V1525M/WT}$). I_{Na} reduction in $Na_V1.5^{V1525M/WT}$ was 24.3% of the tsA201 expressing $Na_V1.5^{WT/WT}$ (n=28 and 23, respectively). tsA201 cells expressing $Na_V1.5^{V1525M/WT}$ did not recapitulate the total loss of I_{Na} observed in iPS-CM. Overall, our results strongly suggest that the mutation $Na_V1.5$_p.V1525M could cause BrS in this family. Moreover, it demonstrates the importance of the use of physiologically relevant models to elucidate the role of $Na_V1.5$ mutations in arrhythmogenic diseases.

Platform: Protein Structure and Conformation IV

2447-Plat

Pathogenic Siderophore ABC Importer YbtPQ Adopts a Surprising Fold of Exporter

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To obtain essential metal ions, human pathogens secrete virulence-associated siderophores at first and then retake the metal-chelated siderophores through a subfamily of ATP-binding cassette (ABC) importer, however, the molecular mechanisms are completely unknown till now. Here, we have determined multiple structures of yersiniabactin importer YbtPQ complex from uropathogenic Escherichia coli (UPEC) at inward-open conformation in both apo and substrate-bound states by cryo electron microscopy. Surprisingly, YbtPQ does not adopt any known fold of ABC importers, but adopt the fold of Type IV ABC exporters. To our knowledge, it is the first time an exporter fold of ABC importer has been reported. In addition, we have observed two unique features in YbtPQ: unwinding of a transmembrane helix in YbtP upon substrate release, as well as tightly associated nucleotide-binding domains without nucleotide bound. Altogether, our study suggests that siderophore ABC importers should be classified as a separate subfamily and have a distinct transport mechanism comparing to others.

2448-Plat

Atomic Structure of the Human Herpesvirus 6B Capsid and Capsid-Associated Tegument Complexes

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Human herpesvirus 6B (HHV-6B), primarily implicated in roseola and neurodegenerative conditions, belongs to the β-herpesvirus subfamily of the Herpesviridae. A hallmark difference of β-herpesviruses from both α-herpesviruses and γ-herpesviruses is the β-herpesvirus-specific phosphoproteins [pU11 in HHV-6B and pUL32/pp150 in human cytomegalovirus (HCMV)], which, in HCMV, forms capsid-associated tegument complexes (CATCs) with multiple functions including securing its large genome of 235-kilobase pairs. To understand capsid assembly, particularly the organization of pU11, here we report the first atomic structure of HHV-6B obtained by cryoEM and sub-particle reconstruction. HHV-6B exhibits high similarity in capsid structure but striking differences in CATC organization when compared to other β-herpesviruses. 180 ''VΔ''-shaped tetrameric CATCs are observed in HHV-6B, distinguishing from the 255 ''Δ''-shaped dimeric CATCs observed in murine cytomegalovirus (MCMV) and the 310 ''Δ''-shaped CATCs in HCMV. This trend in CATC quantity correlates with the increasing genomes sizes of these β-herpesviruses. Incompatible distances revealed by the atomic structures rationalize the lack of CATC's binding to triplexes Ta, Tc, and Tf in HHV-6B. Our results offer insights into HHV-6B capsid assembly and the roles of its tegument proteins, including not only the β-herpesvirus-specific pU11 and pU14, but also tegument proteins conserved across all sub-families of Herpesviridae.

2449-Plat

HIV-1 Pre-Integration Complexes. Structures, Functions and Drug Design

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After retroviral infection of a target cell, during the early phase of replication, the HIV-1 genomic RNA is reverse transcribed by the viral reverse transcriptase to generate the double-stranded viral DNA that interact with viral and cellular proteins to form the pre-integration complex (PIC). Viral integrase (IN) is the key component of the PIC and is involved in several steps of viral replication notably in reverse transcription, nuclear import, chromatin targeting and integration. Viral components such as IN cannot perform these functions on their own and need to recruit host cell proteins to carry out the different processes. IN is a flexible protein with intrinsically disordered regions allowing its interaction with multiple partners and enabling its multiple functions. To study the molecular mechanisms of viral integration we use a bottom - up strategy by assembling *in vitro* and/or *incellulo* multiprotein complexes around the integrase protein (core protein of the PIC). Several complexes have been characterized in our team (IN/LEDGF, IN/LEDGF/INI1-IBD, IN/LEDGF/CA, IN/LEDGF/TNPO3, IN/LEDGF/Nucleosome). To reveal the structure - function relationships of PIC complexes, we combine X-ray, NMR and Cryo-EM structures with biochemical and biological data. Two cryo-EM structures of the IN/LEDGF/DNA and IN/LEDGF/INI1-IBD/DNA complexes have been solved at low resolution (Michel et al., EMBO J., 2009; Maillot et al. PLoS ONE, 2013). With the recent progress of the cryo-EM techniques and our improvement in the complex preparations (Levy et al. Nature Comm. 2016; Eiler et al., Methods in Molecular Biology, 2018) new cryoEM datasets are collected (IN/LEDGF/DNA-pal, IN/LEDGF/Nucleosome) to increase the structure quality to near atomic resolution. In addition, the use of molecular structures together with in vitro assays allows us to develop a screening platform for interaction/allosteric inhibitors with the pre-integration complexes as targets.