KJELDGAARD Lectures - Geoffrey Pitt

Wednesday 21 May 2025 at 14:15-15:00

Followed by PhD-session at 15:30-16:00

(Coffee and cake will be served between lecture and PhD-session)

1871-120 (Nucleus/MBG auditorium)

Host: Chao Sun

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Expanding the roles of Na channel auxiliary subunits

Pathological variants in ion channel pore forming subunits or in their auxiliary subunits cause dysfunction in excitable tissues and consequent disease. Because channel auxiliary subunits often serve additional cellular roles, the physiological significance of variants within channel auxiliary subunits can be challenging to interpret. Fibroblast growth factor homologous factors (FHFs), a subset of the fibroblast growth factor (FGF) superfamily, bind to the cytoplasmic carboxy terminus of voltage-gated sodium channels (VGSCs) and modulate channel function. They are not secreted and do not function as growth factors. While variants in FHFs or VGSCs perturbing their bimolecular interaction are associated with diseases such as cardiac arrhythmias and epilepsy syndromes, alternative cellular roles of FHFs are poorly categorized and thus complicate appreciation of their specific molecular and cellular contributions to disease. Using unbiased proteomics, we uncover alternative functions for FGF13 (the major FHF in mouse heart) in cardiomyocytes that are independent of VGSC function, including regulation of Cx43 gap junctions and hemichannels. With a separation-of-function strategy, we further show that a structurally guided, binding incompetent mutant FGF13 confers complete regulation of VGSC steady-state inactivation (SSI), the canonical effect of FHFs. In cardiomyocytes isolated from *Fgf13* knockout mice, expression of the mutant FGF13 completely restores wild-type regulation of SSI. We show that FGF13 regulation of SSI derives from effects on local accessible membrane cholesterol, which is unexpectedly polarized and concentrated in cardiomyocytes at the intercalated disc (ID) where most VGSCs localize. *Fgf13* knockout eliminates the polarized cholesterol distribution and causes loss of VGSCs from the ID. These results offer new insights into how FHFs affect VGSCs and alter the canonical model by which channel auxiliary exert influence on cellular function.

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