**2-YIA-49** YIA

# Lysosomal Regulation of mTOR-AKT Signaling via the Vacuolar-type $H^+$-ATPase

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Vacuolar-type $H^+$- ATPase (V-ATPase), a multi-subunit protein complex, has two distinct functions on lysosomes: acidifying the lysosomal lumen and controlling mTOR-S6K (mTORC1) signaling via Ragulator. Both functions are crucial for several biological processes. However, little is known about how the functions are coordinated and whether V-ATPase also regulates mTOR-AKT (mTORC2) signaling. We found that knocking down (KD) of a subunit of V-ATPase in human induced pluripotent stem cells (hiPSCs) impaired its functions: increasing lysosomal pH and decreasing mTORC1 signaling. Unexpectedly, the KD also attenuated mTORC2-AKT signaling. Treatment of hiPSCs with bafilomycin A1, a specific inhibitor of V-ATPase proton pump activity, increased lysosomal pH as expected, and decreased both mTORC1 and mTORC2 signaling activities. Therefore, in addition to mTORC1, V-ATPase seemingly regulates the mTORC2-AKT. We are now investigating how V-ATPase regulates mTORC2. Furthermore, we are examining the effects of V-ATPase inhibition on the mTOR signaling *in vivo*. We will discuss our results in this meeting.