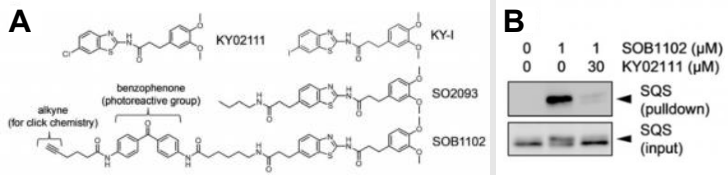
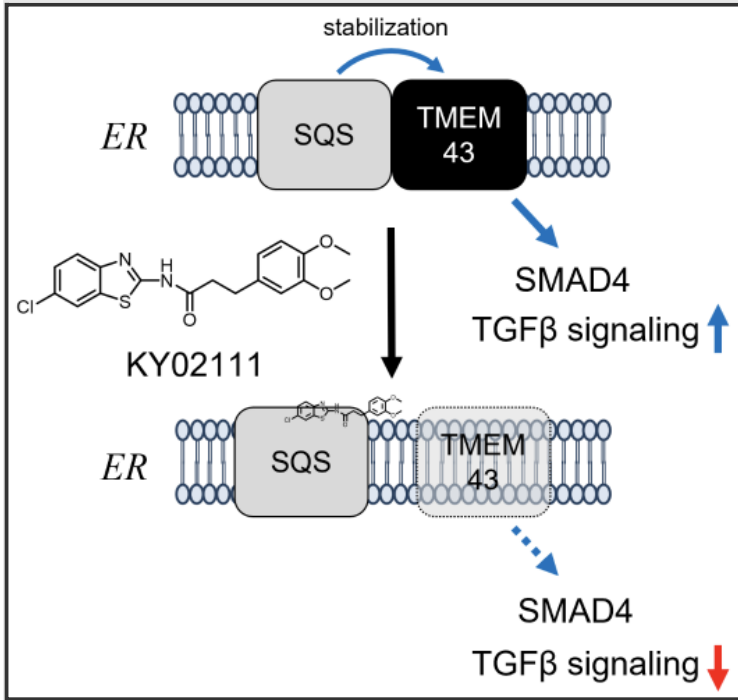




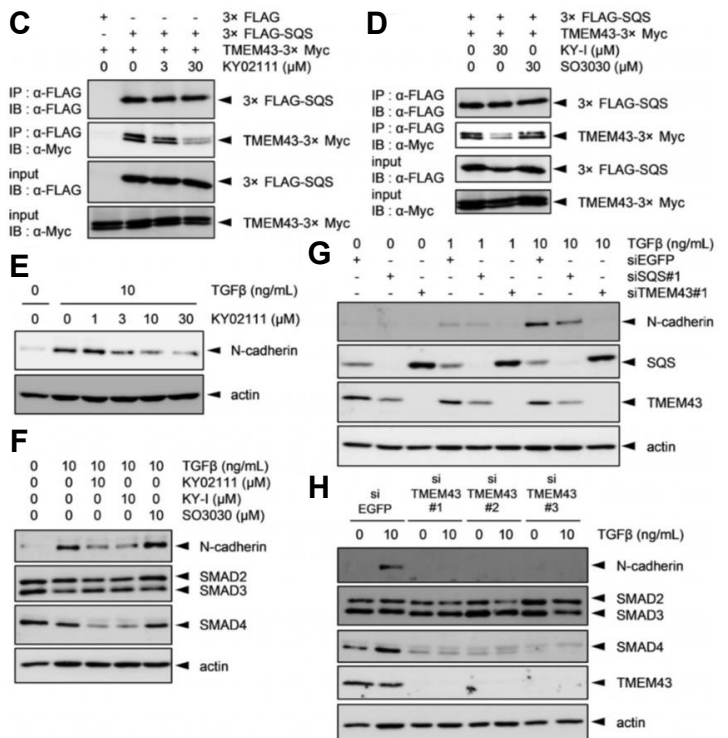
生理活性小分子の新しい世界を切り拓く ケミカルバイオロジー 上杉研究室

化学遺伝学的手法でTGFβシグナルと心筋形成 におけるSqualene Synthaseの役割を解明

Angew. Chem. Int. Ed. 2021, 60, 21824-21831.



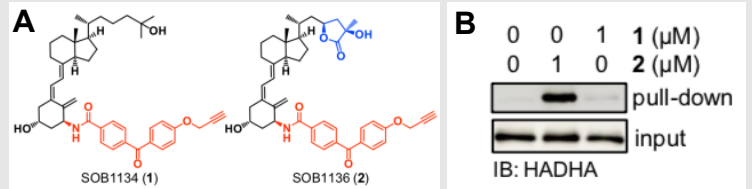
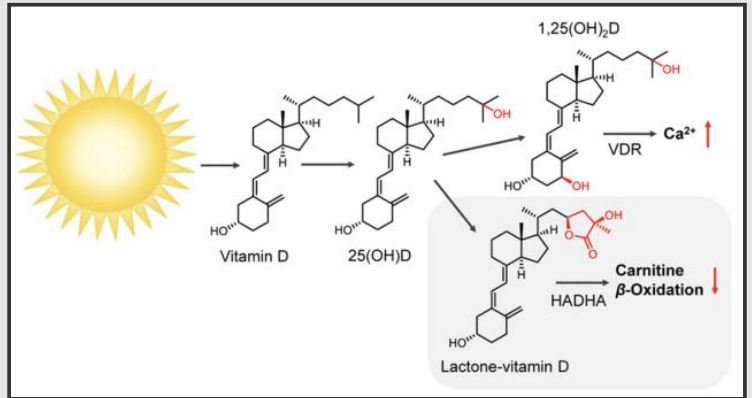
(A) Chemical structures of KY02111, KY-I, SO2093, and SOB1102. (B) Confirmation of photo-reacted SQS. HEK293 cells were pretreated with DMSO or KY02111 (30 μM).



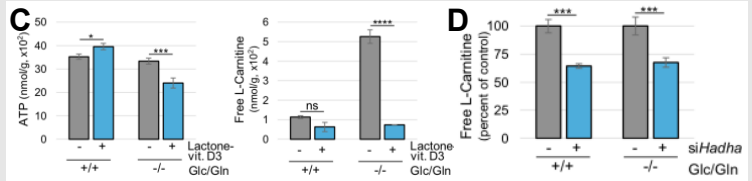
(C, D) Effects of KY02111 and its derivatives on the interaction between SQS and TMEM43. (E, F) Effects of KY02111 and its derivatives on the TGFβ-induced expression of N-cadherin. (G) Effects of SQS/TMEM43 knockdown on the TGFβ-induced expression of N-cadherin. A549 cells were transfected with each siRNA (siEGFP, siSQS, or siTMEM43). (H) Effects of TMEM43 knockdown on the SMADs expression.

ビタミンD代謝物による脂質のβ酸化と カルニチン合成の制御

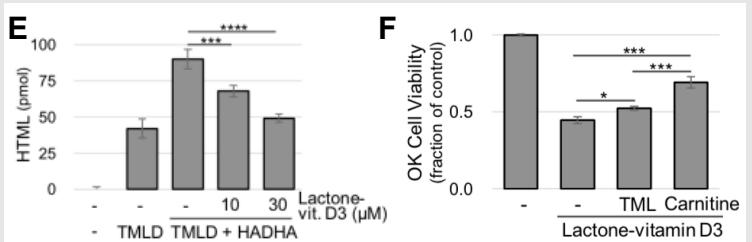
Cell Chemical Biology, DOI: 10.1016/j.chembiol.2021.08.008



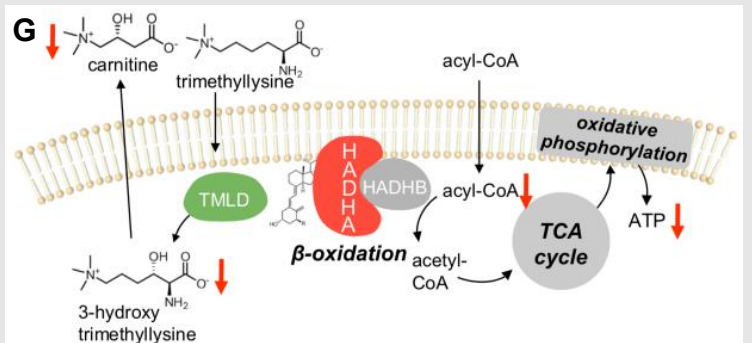
(A) Photoaffinity probes are 25(OH)D3 (SOB1134) and lactone-vitamin D3 (SOB1136). (B) Western blot analysis of probe-HADHA binding interaction.



(C) Metabolite analysis reveals the decrease in ATP and free L-carnitine in the presence of lactone-vitamin D3. Hepa1-6 cells were treated with 30 μM lactone-vitamin D3 for 6 h in medium with (+) or without (-) glucose (Glc) and glutamine (Gln). (D) Western blot analysis of HADHA whose knockdown limits the level of free L-carnitine similar to the effect of lactone-vitamin D3. Hepa1-6 cells were treated with 25 pmol siHadha twice for 48 h each time in medium with (+) or without (-) glucose (Glc) and glutamine (Gln). Lysate was analyzed by immunoblot and carnitine assay.



(E) Impairment of β-oxidation decreases the viability of OK cells that can be rescued by L-carnitine (>50%) and partially by TML. OK cells were incubated with 10 μM lactone-vitamin D3 (7) and 10 μM TML or L-carnitine for 16 h in glucose- and glutamine-depleted medium. (F) TMLD activity is enhanced by HADHA but offset by lactone-vitamin D3. *In vitro* TMLD activity was determined by the production of HTML in the presence or absence of recombinant HADHA and 10 μM compound. HTML was analyzed by HPLC.



(G) Lactone-vitamin D3 binds to HADHA at a site important for HADHA-TMLD interaction, displaces TMLD, disrupts its function, and suppresses carnitine synthesis. The depleted carnitine level compromises fatty acid β-oxidation, leading to the consequent lower cell metabolic activity and ATP production.