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– Chemical Biology –

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Scope of Research

Chemical biology is an interdisciplinary field of study that is often defined as “chemistry-initiated biology.” As biological processes all stem from chemical events, it should be possible to understand or manipulate biological events using chemistry. Our laboratory has been discovering or designing unique organic molecules that modulate fundamental processes in human cells. Such synthetic organic molecules often serve as tools for basic cell biology. Discovery or design of small molecules with unique biological activities permits small-molecule-initiated exploration of complex cellular events. Our mission is to create a new world of bioactive synthetic molecules: new modes of activity, new shapes, and new sizes. We hope to open new avenues for small-molecule applications in a range of fields, including future concepts in drug discovery and use of small molecules for cell therapy.

KEYWORDS

Cell Therapy
Chemical Biology
Small Molecules
Chemical Library
Chemical Genetics

Selected Publications

Asano, L.; Watanabe, M.; Ryoden, Y.; Usuda, K.; Yamaguchi, T.; Khambu, B.; Takashima, M.; Sato, S.; Sakai, J.; Nagasawa, K.; Uesugi, M., Vitamin D Metabolite, 25-Hydroxyvitamin D, Regulates Lipid Metabolism by Inducing Degradation of SREBP/SCAP, *Cell Chem. Biol.*, **24,** 207-217 (2017).

Mao, D.; Ando, S.; Sato, S.; Qin, Y.; Hirata, N.; Katsuda, Y.; Kawase, E.; Kuo, T. F.; Minami, I.; Shiba, Y.; Ueda, K.; Nakatsuji, N.; Uesugi, M., A Synthetic Hybrid Molecule for the Selective Removal of Human Pluripotent Stem Cells from Cell Mixtures, *Angew. Chem. Int. Ed.*, **56,** 1765-1770 (2017).

Katsuda, Y.; Sato, S.; Asano, L.; Morimura, Y.; Furuta, T.; Sugiyama, H.; Hagihara, M.; Uesugi, M., A Small Molecule that Represses Translation of G-quadruplex-containing mRNA, *J. Am. Chem. Soc.*, **138,** 9037-9040 (2016).

Vitamin D Metabolite, 25-Hydroxyvitamin D, Regulates Lipid Metabolism by Inducing Degradation of SREBP/SCAP

Sterol regulatory element-binding proteins (SREBPs) are transcription factors that control lipid homeostasis. SREBP activation is regulated by a negative feedback loop in which sterols bind to SREBP cleavage-activating protein (SCAP), an escort protein essential for SREBP activation, or to insulin-induced genes (Insigs) (endoplasmic reticulum [ER] anchor proteins), sequestering the SREBP-SCAP-Insig complex in the ER. We screened a chemical library of endogenous molecules and identified 25-hydroxyvitamin D (25OHD) as an inhibitor of SREBP activation. Unlike sterols and other SREBP inhibitors, 25OHD impairs SREBP activation by inducing proteolytic processing and ubiquitin-mediated degradation of SCAP, thereby decreasing SREBP levels independently of the vitamin D receptor. Vitamin D supplementation has been proposed to reduce the risk of metabolic diseases, but we have yet to find out the mechanisms. Our results suggest a previously unrecognized molecular mechanism of vitamin D-mediated lipid control that might be useful in the treatment of metabolic diseases.

A Synthetic Hybrid Molecule for the Selective Removal of Human Pluripotent Stem Cells from Cell Mixtures

A major hurdle in stem cell therapy is the tumorigenic risk of residual undifferentiated stem cells. In this, we carried out the design and evaluation of synthetic hybrid molecules that efficiently reduce the number of human induced pluripotent stem cells (hiPSCs) in cell mixtures. The design takes advantage of Kyoto probe 1 (KP-1), a fluorescent chemical probe for hiPSCs, and clinically used anticancer drugs. Among the KP-1–drug conjugates we synthesized, we found an exceptionally selective, chemically tractable molecule that induced the death of hiPSCs. Mechanistic analysis suggested that the high selectivity originates from the synergistic combination of transporter-mediated efflux and the cytotoxicity mode of action. Our study offers a chemical and mechanistic rationale for designing selective, safe, and simple reagents for the preparation of non-tumorigenic clinical samples.