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Chemical genomics for target identification of antifungal theonellamides

Minoru Yoshida

RIKEN Center for Sustainable Resource Science, Japan

Identification of the cellular targets of bioactive small molecules is a major challenge in the development of these molecules as biological tools and therapeutics. Recently, much attention has been drawn to a chemical genetic approach, which uses physical and/or genetic interaction between the compound and its target. Thanks to a wealth of genomic information, genome-wide screening of genetic interaction has become available. We constructed a whole ORF library (ORFeome) of fission yeast and performed reverse proteomics including global analyses of protein subcellular localization (localizome) and protein gel mobility (mobilitome). In combination with these databases and chemical genetic profiling using the strains expressing the ORFeome, we developed a systematic method for drug target identification. This method enabled us to identify the rather unusual mechanism of action of theonellamides (TNMs), marine antifungal cyclic peptides. TNMs were shown to bind to 3 β -hydroxysterols including ergosterol in the fungal cell membrane, thereby inducing abnormal accumulation of 1,3- β -glucan, proving the effectiveness of chemical genomics. Furthermore, we show that in mammalian cells TNMs recognize specific cholesterol-containing membrane domains, induce phase separation of lipid membranes, and induce cell contraction. The usefulness of TNMs as a tool for lipid biology will be discussed.

Biography

Minoru Yoshida received his PhD (1986) from the University of Tokyo, where he worked as Assistant and Associate Professor and accomplished mode-of-action studies on trichostatin A (TSA) and leptomycin B (LMB). He identified histone deacetylase and Crm1 as the specific targets of TSA and LMB, respectively. He moved to RIKEN as Chief Scientist in 2002, and has been playing a leading role in chemical biology. His work has unearthed new targets for drug discovery, and several inhibitors of these targets have come into practical use as anticancer drugs. He received many awards including Japan Academy Prize.

yoshidam@riken.jp

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