微生物サステイナビリティ研究センター
ＭｉＣＳ国際セミナー

日　時：2025年12月18日（木）
15：00～17：00

会　場：筑波大学 総合研究棟 A110
公開講義室

講　師：Associate Prof. Yuichiro Takagi
（Indiana University School of Medicine）

Structural and Mechanistic Characterization of Human Asparagine Synthetase Inhibition by ASX-173: Implications for Cancer Therapy and Microbiology

Abstract

Asparagine metabolism, conserved from microorganisms to humans, represents a fundamental biochemical process central to both microbiology and human disease. Targeting asparagine metabolism is a promising strategy for treating asparaginase-resistant acute lymphoblastic leukemia (ALL), sarcoma, and potentially other solid tumors. Here, we characterize the molecular mechanism by which a cell-penetrable small molecule, ASX-173, inhibits human asparagine synthetase (ASNS), the enzyme that catalyzes intracellular asparagine biosynthesis. ASX-173 reduces cellular asparagine levels, induces the integrated stress response (ISR), and reduces cell growth in HEK-293A cells. A cryo-EM structure reveals that ASX-173 engages a unique, hydrophobic pocket formed by AMP, Mg2+, and pyrophosphate in the C-terminal synthetase domain of ASNS, thereby enabling multivalent, high-affinity binding. Based on in vitro kinetic and thermal shift assays, we find that ASX-173 binds to the ASNS/Mg2+/ATP complex and is therefore a rare example of an uncompetitive enzyme inhibitor with potential therapeutic use. These findings provide a structural and mechanistic basis for targeting ASNS with small molecules, which have application in treating cancer and other human diseases.

主　催：筑波大学 微生物サステイナビリティ研究センター（MiCS）

世話人：小林 達彦（生物機能・教授）

問合せ：admin.mics@un.tsukuba.ac.jp（MiCS事務室）

MiCS Microbiology Research Center for Sustainability

筑波大学 高等研究院 Tsukuba Institute for Advanced Research

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