BL-17A, BL-1A, BL-5A, BL-NW12A, BL-NE3A

レドックス調節パスウェイ酵素群の立体構造解析と創薬(4)

Development of anti-trypanosome drugs targeting nucleotides biosynthesis and red-ox regulatory pathways (4)

○ Emmanuel Oluwadare Balogun[1], Daniel Ken Inaoka[1], Tomoo Shiba[1], Yasutoshi Kido[1], Takeshi Nara[2], Takashi Aoki[2], Teruki Honma[3], Akiko Tanaka[3], Masayuki Inoue[4], Shigeru Matsuoka[4], Paul AM. Michels[5], Shigeharu Harada[6], Kiyoshi Kita[1]

[1]Grad. Sch. of Med., The Univ. of Tokyo; [2]Juntendo Univ. Sch. of Med. [3]System and Struct. Biol. Center, RIKEN; [4]Grad. Sch. of Pharm. Sci., The Univ. of Tokyo; [5]Univ. catholique de Louvain, Belgium; [6]Grad. Sch. of Sci. and Tech., Kyoto Inst. of Tech.

Human African Trypanosomiasis is caused by *Trypanosoma brucei gambiense* (Tbg) and *T. b. rhodesiense*. It is a threat to 60 million human lives. Currently available treatments have become unsatisfactory, hence the need for development of new chemotherapies. Our laboratory has found ascofuranone (AF) to be a promising drug candidate for the disease. AF is an excellent inhibitor of trypanosomal alternative oxidase; however, its potential to kill trypanosomes is considerably enhanced when co-administered with 5 mM glycerol. This synergistic effect mediated via glycerol kinase (GK) inhibition results in blockade of ATP generation. This required concentration of glycerol for co-administration with AF is unphysiological for the host. Although GK is promising target of chemotherapy, an effective and selective parasite GK inhibitor is yet to be available, structural study is helpful for inhibitor design. In this study, TbgGK was overexpressed in *Escherichia coli*, purified to homogeneity, and crystallized. Complete X-ray diffraction data sets were collected to 2.90, 2.40, 2.80, 1.90, and 2.0 Å resolutions respectively for Apo, glycerol, glycerol 3-phosphate, ADP, and ATP forms of TbgGK. Some of the distinctive structural features observed in TbgGK include additional loops around the active site and an ADP/ATP binding site that is not found in other GKs. Also, a structural dynamics that is mediated by a disulphide linkage involving Cys278 and Cys319 was observed to precede glycerol binding. Using the solved structures for *in silico* screening, an encouraging number of inhibitors with novel scaffold have been identified.