光親和型リンカーと親水性 HPMA 共重合体を用いた生理活性物質の標的同定

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我々が化合物ビーズに利用している光親和型リンカー（フェニルジアジリン）を用いて、生理活性物質の標的同定をする方法論の論文がチェコのグループから発表されており、我々の化合物ビーズとは何が違うのか知るために、今回この論文を紹介する。チェコのカレル大学の Konvalinka のグループは、プロテアーゼの阻害剤の研究と、親水性 HPMA 共重合体(copolymer)を用いた合成抗体 iBodies の研究を行っており、この親水性 HPMA 共重合体と光親和型リンカーを組み合わせてこの論文では使用している。ビーズによる標的同定だけでなく、この親水性 HPMA 共重合体は、細胞内にも取り込まれ、細胞内での標的の可視化にも利用できる。

紹介論文

Identification of protein targets of bioactive small molecules using randomly photomodified probes.
Petr Šimon, Tomáš Knedlík, Kristýna Blažková, Petra Dvořáková, Anna Březinová, Libor Kostka, Vladimír Šubr, Jan Konvalinka, and Pavel Šácha
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ACS Chemical Biology **13**, 3333-3342 (2018).

要旨

Identifying protein targets of bioactive small molecules often requires complex, lengthy development of affinity probes. We present a method for stochastic modification of small molecules of interest with a photoactivatable phenyldiazirine linker. The resulting isomeric mixture is conjugated to a hydrophilic copolymer decorated with biotin and a fluorophore. We validated this approach using known inhibitors of several medicinally relevant enzymes. At least a portion of the stochastic derivatives retained their binding to the target, enabling target visualization, isolation, and identification. Moreover, the mix of stochastic probes could be separated into fractions and tested for binding affinity. The structure of the active probe could be determined and the probe resynthesized to improve binding efficiency. Our approach can thus enable rapid target isolation, identification, and visualization, while providing information required for subsequent synthesis of an optimized probe.

参考論文

iBodies: Modular synthetic antibody mimetics based on hydrophilic polymers decorated with functional moieties. Pavel Šácha, et al., and Jan Konvalinka.
Angew. Chem. Int. Ed. **55**, 2356-2360 (2016).