28M-pm15S

膜透過性核酸の開発

○Zhaoma SHU[1], 太田 杏積[1], 田中 育[1], 伏原 大地[1], 阿部 奈保子[1], 友池 史明[1], 木村 康明[1], 阿部 洋[1,2]（[1]名大院理, [2]理研）

[Objectives]: Oligonucleotides repress gene expression in a sequence-specific manner, their medical applications are expected. These therapeutic oligonucleotides contain: (1) Antisense DNA; (2) Small interference RNA (siRNA). But their extreme low cell permeability requires effective delivery methods. In this research, we developed a kind of cell membrane permeable oligonucleotides which is promising for broad application.
[Molecular Design]: Recently, disulfide moiety was found to promote cellular permeability efficiently because of the thiol-disulfide exchange reaction between the thiol/disulfide group of proteins on cell membrane. Therefore, similar linkers terminated with disulfide moiety can be used in membrane permeable oligonucleotides design. Due to diversity of reaction activity, we designed four kinds of disulfide moiety.
[Methods]: Phosphoramidite chemistry is widely used for oligonucleotides synthesis. It can be manipulated easily and efficiently on automatic DNA synthesizer. Thus, our disulfide linker with a phosphoramidite reaction center can be attached to the DNA or RNA strand at any desirable position with different repeats. We designed our sequence targeting firefly luciferase and tested the gene silencing effect in HeLa cells that stably expressed the firefly & renilla luciferase gene.
[Results]: We attached our four kinds of disulfide linker on phosphorothioate backbone DNA and siRNA with different repeats. These oligonucleotides equip significant cell membrane permeability and exhibit satisfying gene silencing efficiency.
[Prospect]: After getting the significant results *in vitro*, we are going to examine the effect *in vivo* with mice and investigate how is its cellular uptake and endosome escape to elucidate the deeper mechanisms.