Design of cell penetrating nanoparticle for drug delivery. An amphipathic α-helical peptide co-assembles into nanoparticle

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The Cell penetration properties of peptides are interesting behaviors in that large molecules penetrate into the cells. Peptide aggregation and self-assembly are known to regulate biological functions, including cell penetration. However, it is not well known that cell penetrating property of peptides is related to their tendency to agglomerate (or oligomerize). Although we reported in a previous paper that the oligomerization tendency of an amphipathic peptide may be related to their cell penetration ability, there was no direct evidence for oligomer formation at nanomolar concentrations at the cellular level. In this presentation, we report the results of more effective fluorescence resonance energy transfer (FRET) of a dimeric bundle peptide, LK-3, in cells than that of the monomeric peptide, LK-2. Next, we used X-ray crystallography to determine the atomic structures of oligomers form by LK-3 and the derivative. These α-helical disulfide bundle peptides form hexamers, the trimer of dimers. These structures demonstrate that the dimer subunits are further associated to form a hydrophobic core. Also using the enantiomeric relationship between L-form dimer LK-3 and D-form dimer lk-3, we discovered that the 1:1 mixture of L/D-peptide dimers shows c.a. 30% increase in cell penetrating comparing to each enantiomerically pure peptide. Given that the enantiomeric mixture of α-helical peptides promotes the formation of oligomers to enhance cell penetrating abilities, oligomerization is related to the cell penetrating behavior of the amphipathic α-helical peptide in the cellular level. Consequently, we report direct evidence of the fact that the amphipathic peptide LK-3 forms oligomers in cells at low nanomolar concentrations.

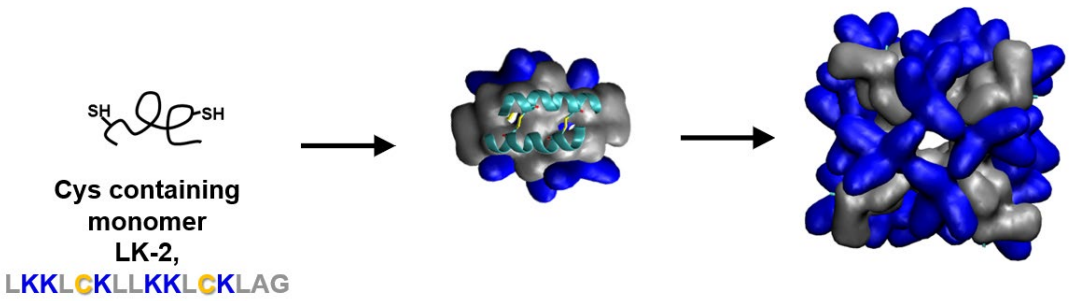

Figure 1. Your figure caption may be placed here. Delete this text box if not used.

References

[1] Hyun, S.; Lee, Y.; Jin, S. M.; Cho, J.; Park, J.; Hyeon, C.; Kim, K.-S.; Lee, Y.; Yu. J. *ACS Central Sci.* **2018**, *4*, 885-893.