Cell Penetrating Peptides

Most prospective therapeutic and diagnostic agents have very poor cell permeability and bioavailability. Cell penetrating peptides (CPPs), also known as protein transduction domains, have the ability to translocate through the cell membranes. As such, they have received formidable attention in the current advances in drug delivery as promising tools to overcome drug delivery problems. These peptides have been used to deliver drugs, imaging agents, and other therapeutic biomolecules across the cell membrane into the cytoplasm.

References
1. Richard et al., J. Biol. Chem. 2003, 278, 59-59
2. Fonseca et al., Advanced Drug Delivery Reviews, 2009, 61, 959-964

Commonly Used CPPs

| Peptide                  | Sequence                          |
|-------------------------|-----------------------------------|
| HIV-1 TAT 48-60          | GRKKRRQRRPPQ                      |
| Antennapedia 43-58 (Penetratin) | RQIKIWFQNRRMKWKK                  |
| Transporter             | GKTWVETWTVWGSQPVKVR               |
| Polyarginine            | RRRRRRRRRRR                       |
| Pep1                    | KETVWETWTVWGSQPVKVR               |
| BMV Gap (T-23)          | KMATNCRARAAARRRARRRSTAR           |

Table 1. Sequences of commonly used penetrating peptides

Polyarginines

Oligoarginines of 6-20 residues have been studied extensively for their ability to penetrate into cytoplasm through the cell membrane. It was found that optimal cell membrane permeation is achieved by oligoarginines residues between 5 and 15.1 In particular, nona-arginine peptides were shown to have improved cell penetration efficiency compared to TAT peptides.2 Thus, most studies have utilized octa- and nona-arginine peptides as delivery medium for most biological molecules including uRNA, anticancer drugs, small molecules, proteins, and oligonucleotides.3,4 Since oligoarginines peptides are the most commonly used CPPs, their optimization to reduce cell toxicity and improve protelation stability has been investigated. Replacement of L-arginines with D-arginine residues results to protect resistant polyarginines with better intracellular translocation compared to L-oligoarginines peptides.5 In addition, fatty acids have been incorporated to generate more active peptides with low toxicity. Lee et al. incorporated C14 fatty acid chains. The resulting lipo-oligoarginines had minimal cell adhesion and uptake have also been designed by incorporating a polylysine chain as a counter ion domain. The protein table linker between the polylysine domain and polyarginine domain results in the cell translocation.6 It has been portrayed that the guanidino functional group plays a critical role in the intracellular translocation of oligopeptides. Hence, several other guanidino containing molecules have been discovered. Wender et al., designed a polyarginine peptide derivative with improved metabolic stability and minimal cytotoxicity.1 A peptide with minimal cell adhesion and uptake have also been incorporated to design a polylysine chain to translocate into the cell membrane.7

References
1. Bonduelle et al., Peptides. 2000, 21, 113-125
2. Tung and Weissleder, Adv. Drug Del. Rev. 2003, 55, 281-290
3. Vives et al., J. Pept. Res. 2010, 75, 429-439
4. Aguilera et al., Pharmaceuticals. 2010, 3, 2049-2055
5. Aguilera et al., J. Pept. Res. 2010, 75, 429-439
6. Aguilera et al., Pharmaceuticals. 2010, 3, 2049-2055
7. Aguilera et al., Pharmaceuticals. 2010, 3, 2049-2055

Antennapedia 43-58 (Penetratin)

Antennapedia 43-58, a 16 amino acid fragment from the third helix of Drosophila antennapedia, was shown to have the capability of translocating through cell membrane.2 Similar to TAT peptides, antennapedia have been used as a delivery system of various cargo through the cell membrane into the cytoplasm. Villa et. al. studies have shown that penetratin-PNA constructs effectively translocates into melanoma cells.8 More studies by Avignolo et al. have used antennapedia to transport monoclonal antibodies into the colorectal carcinoma cell lines (HCT116).9

References
1. Bonduelle et al., Peptides. 2000, 21, 113-125
2. Tung and Weissleder, Adv. Drug Del. Rev. 2003, 55, 281-290
3. Tung and Weissleder, Adv. Drug Del. Rev. 2003, 55, 281-290
4. Wender et al., designed a polyarginine peptide derivative with improved metabolic stability and minimal cytotoxicity.1 A peptide with minimal cell adhesion and uptake have also been incorporated to design a polylysine chain to translocate into the cell membrane.7

Other Drug Delivery Techniques

Dendrimers: These molecules have unique features such as high loading capacities for bioconjugation and uniformity. Thus, they have received considerable attention in biomedical field as drug delivery systems for drugs and imaging agents.1 Dendrimers with guanidine modifications have been investigated as delivery systems for DNA, RNA, nanoparticles, proteins and small molecules such as dyes, in different cell lines. Dendrimer cargo can be incorporated either in the cavities or covalently bound to the dendrimers using different chemistries.

References
1. Bonduelle et al., Pharmaceuticals. 2010, 3, 2049-2055
2. Tung and Weissleder, Adv. Drug Del. Rev. 2003, 55, 281-290
3. Tung and Weissleder, Adv. Drug Del. Rev. 2003, 55, 281-290
4. Wender et al., designed a polyarginine peptide derivative with improved metabolic stability and minimal cytotoxicity.1 A peptide with minimal cell adhesion and uptake have also been incorporated to design a polylysine chain to translocate into the cell membrane.7

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