pH-dependent linkage, thus allowing CsA to be released at physiological pH. The conjugate efficiently penetrated into the skin so that it was detected not only in epidermis and dermis but also in T lymphocytes in the dermis, although the water solubility, as well as polarity of the conjugate, was substantially more than that of CsA alone.

Gautam et al. (2016) reported that IMT-P8 (15 amino acid residues in length) as a CCP mediated delivery of KLA (a proapoptotic peptide) and GFP (green fluorescent protein) into the human tumor cells, as well as epidermis layer and hair follicles. KLA is a cationic amphipathic peptide with 14 amino acid residues, which could disturb the mitochondrial membrane, but it does not alone enter the cell and also the skin in the intact form. Recombinant protein GFP is a 27-kDa macromolecule and similar to KLA could not permeate across the cell membrane or skin barrier on its own. However, conjugation with IMT-P8 increased permeation of KLA and GFP across mouse skin. Similar to this report, the successful topical delivery of GFP by conjugation to the POD peptide and accumulation of conjugate into the epidermis and hair follicles were reported by Johnson et al (2010). It is suggested that some CPPs enter the skin layers through a transfollicular route (Gautam et al. 2016).

According to these studies, it can be said that CPPs exert their actions through different mechanisms, and depending on the molecular size, hydrophobicity, electrical charge, secondary structures, and so on, different mechanisms could be proposed for their permeation. Finally, it seems that CPPs are an attractive, powerful, and promising tool to overcome the skin barrier.

34.4 CONCLUSION

As therapeutic and cosmetic peptides and proteins are developing, appropriate and noninvasive delivery strategies should also be developed. Transdermal delivery of peptides and proteins could be a convenient alternative to the parenteral route. As highlighted here, attaining efficacious skin delivery of peptides and proteins (either topical or transdermal) is a laborious task. Chemical modification is one of the effective approaches to overcome the barrier properties of skin. The results of studies performed so far suggest that covalent conjugation of a hydrophobic moiety or CPP to macromolecules could mostly enhance the skin permeation of peptides and proteins. CPPs seem to be more potent in increasing skin permeation, at least about proteins in comparison to hydrophobic moieties. However, skin side effects of both moieties should also be evaluated. Chemical modifications not only increase skin permeation ability but also increase the metabolic stability of peptides and proteins in the skin. However, it might be possible that covalent conjugation leads to a decrease of biological activity, but not so much that the peptide or protein activity is completely eliminated. Of course, it's presumed that reducing activity will be neutralized by increased penetration and stability. Given these findings, it seems that chemical modification will have a major impact on the topical and transdermal delivery of peptides and proteins.

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