Transcellular peptide-drug conjugate as an effective PDE4 inhibitor for psoriasis-like inflammation

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Peptide-drug conjugates (PDCs) have emerged as a promising class of drug delivery systems, combining carrier peptides with therapeutic agents to enable efficient delivery to target sites. Overcoming biological barriers, such as the blood-brain barrier and epithelial barriers, remains a significant challenge for effective drug delivery. In this study, we aimed to enhance transcellular delivery of PDCs by developing transcellular peptides that integrate the advantageous characteristics of both cell-penetrating peptides (CPPs) and antimicrobial peptides (AMPs). Through a comprehensive analysis of CPPs, including physicochemical factors, we identified a group of CPP-like AMPs. Multiple sequence alignment (MSA) and the basic local alignment search tool (BLAST) guided the selection of 16 candidate transcellular peptides from natural sources. Among the candidates, SDT7 demonstrated superior cell permeability and enhanced kinetic profile in human keratinocytes. Furthermore, SDT7 exhibited notable skin permeability in human cadaver skin and mouse skin. Building upon this discovery, we developed a peptide-drug conjugate by combining SDT7 with the ginger-derived compound 6-Paradol (PAR). The resulting SDT7-PAR complex, named TM5, demonstrated enhanced skin penetration efficiency and exhibited anti-inflammatory effects in psoriasis mouse models. These findings highlight the potential of novel transcellular PDCs with transcellular peptide SDT7 in overcoming biological barriers for therapeutic applications.