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PTD-mediated delivery of anti-cell death proteins/peptides and therapeutic enzymes ☆

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Abstract

Millions of unnecessary cells are removed from our body everyday by apoptosis to ensure our survivals. Apoptosis is a highly coordinated process. Failure in apoptotic regulation results in disease. A large number of studies have demonstrated that accelerated apoptosis is involved in degenerative diseases, ischemic injuries, immunodeficiency and infertility. These studies have also revealed the molecular mechanisms of apoptosis signal transduction to provide therapeutic targets. On the other hand, protein transduction technology has been developed to deliver full-length proteins to various tissues including the brain. So far, many studies have shown that *in vivo* delivery of therapeutic proteins/peptides, including anti-apoptotic proteins, an anti-oxidant enzyme, a neuroprotectant, enzymes involved in purine or tyrosine metabolism, caspase inhibitors, c-Jun N-terminal kinase inhibitors and an NF-κB inhibitor, by protein transduction technology mitigates various diseases in animal models.

Keywords: Apoptosis; Bcl-2 family; Enzyme replacement; Ischemia/reperfusion injury; Necrosis; Neurodegenerative diseases; Peptide inhibitors; Protein therapy

Contents

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1. Introduction

Apoptosis is a biological process of immense importance and is physiologically essential for normal development and tissue homeostasis in adults to regulate the balance between proliferation and cell death; therefore, dysregulation of apoptosis can lead to disease. Apoptosis is known or suspected to contribute to acute diseases, such as stroke, heart attack and liver failure, through inducing massive cell death in tissues or organs, and to certain slow-progressing diseases, such as Parkinson's disease. As apoptosis machinery is equipped in almost all cells of our body, it is an attractive target of therapeutic intervention. It is known that a wide range of stimuli, regardless of intra-cellular or extra-cellular stimuli, can induce apoptosis, which is regulated in different ways from cell to cell, and is carried out in a stimulus- and cell type-dependent manner. The common components of the apoptosis mechanism are finally activated in the execution of apoptosis.

For successful systemic drug delivery, it is important to pass through difficult barriers, such as the cellular membrane or specialized cellular barriers, for example, the blood–brain barrier. After several observations that HIV-1 Tat protein [1,2] and homeodomain protein Antennapedia [3,4] can enter cells, many peptide sequences, the protein transduction domain (PTD) or cell-penetrating peptide (CPP), have been identified to be responsible for membrane translocation. The finding that systemically administered TAT-fused β-galactosidase is delivered into the brain [5] has encouraged studies in delivering therapeutic proteins/peptides. This article is intended to review studies on systemic delivery of anti-cell death proteins/peptides intervening in apoptosis