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Mini-review

Methods for engineering therapeutic peptides

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Graphical Abstract

This review discussed recent advancements related to therapeutic peptide engineering.

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ABSTRACT

Peptides are a class of drugs that have become increasingly important and influential for the treatment of many human diseases. Compared to traditional small molecule drugs, peptides have the potential for higher target specificity and potency, along with better safety profiles. On the other hand, the complex and fragile nature of peptides poses significant challenges for their administration. Of particular concern is that they are often unstable and can be rapidly degraded by various proteases after dosing. To address these inherent problems of peptides, many different methods have been attempted. Here, we briefly review these methods, with an emphasis on the effect of each method.

1. Introduction

Contemporary drugs can be roughly classified into three broad categories: traditional small molecule drugs, large biologics and medium-sized peptides between the two. Since 1922, when insulin was first developed for the treatment of diabetes, peptides have become recognized as a critical drug class for areas where small molecules are ineffective. This middle-ground class has several advantages over the other categories. Compared to small molecule drugs, peptides have the potential for higher target specificity and potency, along with better safety profiles; and compared to large biologics, small peptides are cheaper to produce because of easier standardization and quality control [1].

Peptides are typically defined as small proteins of up to 50 amino acids. More than 7000 peptides have been identified so far from a wide variety of natural sources. They have evolved to play important and diverse roles in human physiology. They can provide a first line of defense against invading microorganisms, act as ligands of membrane receptors and ion channels, and serve as a means of intercellular communication in the form of hormones, neurotransmitters, and growth factors. The versatile biological activities of peptides, together with the fact that they generally have high specificity, potency, and safety, yet low toxicity, make them attractive candidates for development as therapeutics. More than 60 peptides are currently approved or in the process of final approval for the treatment of human disease, most commonly indicated for metabolic disease and oncology [2]. With more than 600 peptide molecules in clinical and preclinical development, the number of peptide therapeutics is expected to quickly expand in the near future. However, peptides have a distinct set of limitations compared to small-molecules, the most prominent of which is high susceptibility to acid/base hydrolysis and proteolytic degradation [2]. Because of this low stability and other issues like aggregation, there still remain many peptides with significant therapeutic potential that have not been successfully developed into clinical stage drugs despite many years of sustained effort. Therefore, optimizing peptide properties through engineering represents a major and important step for improving the therapeutic use [3].

Many different methods, including peptide conjugation, fusion, glycosylation, cyclization, and mutation have been pursued to improve therapeutic properties of peptides. These approaches have varying degrees of success in extending the circulatory half-lives of peptides, improving their properties like proteolytic stability, solubility, absorption through biological membranes, and decreasing their aggregation propensity. In this mini-review, we mainly focus on the comparison of the methods used for optimizing these properties.

2. Circulatory half-life extension