Commentary

Pharmaceutical BIOPROCESSING

Optimization of Protein Therapies by Polymer-Conjugation

Abstract

Recent advances in unwellness genetics, several disease-related proteins are found. It's expected that there'll be therapeutically helpful proteins among them. However, it's clinically troublesome to use most proteins as effective and safe medication thanks to their terribly low stability and pleiotropic actions in vivo. To market unwellness proteomic based mostly drug development for macromolecule therapies, we've got tried to develop an optimum polymer-conjugation system for up the therapeutic efficiency of proteins. During this review, we tend to introduce this innovative protein-drug system.

Keywords: PEGylation• polyvinyl pyrrolidone• Tumor necrosis factor-alpha• Interluekin-6

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Received: 01-Jul-2022, Manuscript No. fmpb-22-50107; **Editor assigned:** 04-Jul-2022, PreQC No. fmpb-22-50107 (PQ); **Reviewed:** 15-Jul-2022, QC No. fmpb-22-50107; **Revised:** 22-Jul-2022, Manuscript No. fmpb-22-50107 (R); **Published:** 29-Jul-2022 , DOI: 10.37532/2048-9145.2022.10(4).70-71

Introduction

The success of the human genome project, the focus of life science research has shifted to the functional and structural analyses of proteins, such as disease proteomics. Therapeutic application of bioactive proteins, such as newly identified proteins and cytokines, are also promising [1].However, because these proteins are generally quite unstable in vivo, their clinical application requires frequent administration at high dosages. In recent years, to overcome these problems, the conjugation of proteins with water soluble polymeric modifiers has been developed, especially, the conjugation with polyethylene glycol (PEG), often called "PEGylation". Bio conjugation of proteins with water-soluble polymeric modifiers increases their molecular size and steric hindrance, both of which are dependent on the polymeric modifiers attached the proteins. These effects improve the plasma half-lives of proteins and their stability against proteolytic cleavage, and also decrease their immunogenicity [2]. This allows the therapeutic dose and frequency to be decreased.

Description

Conjugation with a polymeric modifier inhibits the transport from blood to tissues and the binding to their receptors. In addition, specific activities of proteins are decreased by the attachment of polymeric modifiers to active sites [3]. Therefore, determination of the relationships among the degree of modification, molecular size, and specific activity is very important to optimize the modification-condition, which enable designing of polymer-conjugated proteins applicable to clinical use. For further enhancement of the therapeutic potency and safety of polymer-conjugated proteins, more precise control of the in vivo behavior of each protein is necessary for selective expression of their therapeutic bioactivities. We found that polymer-conjugated proteins can be greatly affected by the properties of the polymeric modifiers attached to the surface of the proteins. Therefore, it is necessary to identify appropriate polymeric modifiers for design of conjugated proteins with desirable in vivo behavioural characters [4]. PEG is a low toxicity and low antigenicity polymeric modifier that has been used frequently for conjugation of proteins. From the viewpoint of a drug delivery system, PEG, however, also have some disadvantages as a

drug carrier, principally the fact that PEG only has a functional group at the end of the chain, limiting the possibilities of adding new functions to the drugs to control more precisely their pharmacokinetics and tissue distribution. The blood and specific damage to the tumor vessels. In addition, in the process of bleeding necrosis in the tumor vessels, the vascular permeability of the tumor vessels is selectively increased, promoting transport from blood to the tumor tissue. Therefore, improvement in blood stasis may enhance all anti-tumor action mechanisms of TNF-alpha increasing its bio availability. Therefore, we performed conjugation of the lysine amino residues of TNF-alpha using PEG. Thus, in bioactive proteins such as TNF-alpha, IL-6 and LIF that require binding to a receptor for the expression of activity, consideration should be given to inhibition of activity derived from inhibition of binding to receptor molecules caused by steric hindrance by the polymeric modifier, in addition to a decrease in the specific activity due to modification of the lysine residues. On the other hand, the in vivo anti-tumor effects of PEGylated TNF-alpha were the most marked for MPEG- TNF-alpha. t they are abundant on the pulmonary vascular lumens and on the outer surfaces of marrow veins [5]. Therefore, if IL-6 is modified to remain longer in the blood and thus smaller dose levels are required for therapeutic use, it will be possible to make the in vivo distribution and receptor affinity of IL-6 such that a selective and efficient action of IL-6 on megakaryocytes can be achieved. Thus, we attempted the conjugation of IL-6 with PEG, to increase in the activity of IL-6 in the promotion of platelet production and to reduce its side effects. When IL-6 was subjected to PEGylation under optimum conditions, selected by consideration of the relationships between specific activity, degree of PEG-modification, molecular size, etc., the resultant PEG-modified IL-6 (MPEG-IL-6) showed plasma half-life more than 100 times greater than that of native IL-6. MPEG-IL-6 showed more than 500 times the thrombopoietic potency of native IL-6. We have thus succeeded in making cytokines useful as therapeutic agents by improving their stability in vivo and increasing in selected favourable actions (anti-tumor activity in the case of TNF-alpha and the promotion of platelet production in the case of IL-6). These results suggested that polymer-conjugation is a pragmatic approach to successful therapies with various bioactive proteins and peptides.

Acknowledgement

None

Conflict of interest

No conflict of interest

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