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Gene therapy of cytokinins and its growth factors

P Chuan*

Department of Microbiology, Maharshi Dayanand University, Rohtak, India

*Corresponding author. E-mail: pratyooshchuan@gmail.com

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DESCRIPTION

The utility of cytokines and growth factors acting as receptor agonists is limited by their short half-lives in circulation and poor transport across the Blood Brain Barrier (BBB). They show that by genetically inserting macro cyclic peptide pharma cophores into the structural loops of a human immunoglobulin's Fragment Crystallizable (FC) region, they can generate surrogate receptor agonists with longer half-lives in circulation and increased transport rates across the blood-brain barrier.

Furthermore, lasso-grafting the mouse anti-transferrin-receptor antibody FC region with met-binding macro cyclic peptides increased the accumulation of the resulting met agonists in brain parenchyma. Lasso-grafting may enable the development of designer protein therapeutics with improved stability and pharmacokinetics. The US Food and Drug Administration has approved the clinical use of cytokines and growth factors as therapeutics, and their potential application in emerging areas such as neurogenesis and brain repair is a focus of intense research. However, their inherent structural properties make it difficult to engineer for improved physicochemical stability and pharmacokinetics, particularly for better half-life or BBB penetrance.

Polyethylene glycol conjugation and fusion with the fragment crystallisable region of immunoglobulin to extend their half-lives; and fusion with the fab of the anti-Transferrin Receptor (TFR) antibody to enhance their penetration across the BBB are existing methods for controlling the pharmacokinetics of protein therapeutics. However, the extent to which these methods can improve protein pharmacokinetics without impairing bioactivity is dependent on the properties of each protein. Surrogate agonists that are structurally unrelated to native ligands have been developed to overcome the inherent structural limitations of cytokines and growth factors. Despite recent advances, there is still a significant unmet need for more robust and versatile methods for designing protein therapeutics with desired physicochemical stability and pharmacokinetics.

Macrocyclic peptides have emerged as a promising novel class of drug candidates, with desirable properties such as antibody-like binding affinity and specificity, the ability to target unique chemical spaces. Because of their constrained cyclic structures, macrocyclic peptides have higher affinity for targets than linear peptides. An intriguing possibility for expanding the applicability of these macrocyclic peptides is to 'engraft' them onto protein scaffolds, allowing for functional peptide-protein combinations.

The RaPID (Random Non-Standard Peptides Integrated Discovery) system, which combines messenger RNA display and genetic code reprogramming, has enabled the discovery of thioether-based cyclized macrocyclic peptides with high binding specificity to target proteins. Previously, they demonstrated that RaPID-derived pharmacophore sequences can be easily implanted onto surface-exposed loops of proteins while maintaining both the functions of the guest peptide and the host protein, a process they called lasso-grafting. The observed exceptional grafting compatibility is most likely due to the pharmacophore motifs' intrinsic ability to self-fold into target-binding conformations similar to the parental macro cycle, even in the context of the scaffold proteins' unrelated loop structure.

As a result, the choice of scaffold protein is critical, as it determines the success of peptide grafting while also conferring desirable properties to the engineered products such as metabolic stability and cell permeability. Disulfide-stabilized peptides and mini proteins have been engineered to act as specialised scaffolds for peptide grafting to accommodate this wide range of desirable properties. These specialised scaffolds, however, are small non-human proteins with no unique bioactivities.

Although natural human proteins are desirable scaffolds for peptide grafting, attempts to graft *de novo* identified

peptides onto natural human scaffolds have been very limited thus far. Grafting synthetic *de novo* identified peptides into an independently folded domain of a natural scaffold frequently results in mis-folding and inactivation of both entities. As a result, their preliminary findings indicate that functional grafting of *de novo* identified macrocyclic peptides into the protein loops of natural scaffolds is far more feasible than previously thought.