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Mini Review

Pharmacokinetics and Biodistribution Effects of certain Fusion Proteins on Recombinant Protein Polymer and Antibody

Emily Antonio*

Department of Chemical and Biomolecular Engineering, USA

*Corresponding Author's E-mail: antonioemily@rediff.com

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Abstract

There is growing evidence that protein domains or inherently unstructured proteins serve crucial biological purposes. The polymer theory, which was created to forecast the general physical characteristics of polymers, can be usefully used to the analysis of these kinds of proteins. These theories "coarse-grain" the molecular information out of the models and replace it with a few of constants that define the polymer. This decrease in complexity makes it possible to study very large systems. The time scales that are available also greatly expand in the case of simulations. Here, we talk about how unstructured proteins can be categorised within a polymer framework and how polymer theory can be applied to them. In order to predict functionally significant properties like gyration radius, height of a polymer brush, and force needed to compress a polymer brush, we then review polymer theory (Pavia et al., 2020).

Alternative non-IgG binding proteins created for therapeutic purposes are compact and, as a result, are quickly removed from the bloodstream by renal filtration. Extensions of unfolded polypeptides have been developed to prolong serum half-life in order to avoid repeated injection or continuous infusion for the maintenance of therapeutic serum concentrations, but systematic, comparative studies examining the impact of their size and charge on serum half-life, extravasation, tumour localization, and excretion mechanisms have yet to be conducted (Gurusamy et al., 2013). In a preclinical tumour xenograft model in mice, we employed a high-affinity Designed Ankyrin Repeat Protein (DARPin) targeting the tumour marker epithelial cell adhesion molecule (EpCAM) and fused it with a number of predetermined unstructured polypeptides. We did a detailed comparative localization, distribution, and extravasation investigation using three different sizes of two previously known polypeptides—an uncharged one called PAS that only contains Pro, Ala, and Ser and a charged one called XTEN that contains Pro, Ala, Ser, Thr, Gly, and Glu. With a half-life of up to 21 hours in mice, pharmacokinetic study demonstrated a clear linear association between hydrodynamic radius and serum half-life for both polypeptides. EpCAM was required for tumour uptake, which was directly correlated with half-life and tumour growth and demonstrated uniform tumour penetration for all fusion proteins without unintended accumulation in non-target tissue. Unexpectedly, charge had no effect on any measure, including renal elimination kinetics, tissue accumulation, tumour, or tissue accumulation. Thus, the potential for precise half-life alteration and tumour targeting is essentially similar for both types of polypeptides (Banani et al., 2017).

Keywords: Biodistribution, Darpin, Half-life extension, pasylation, Tumor targeting, Xtenylation

INTRODUCTION

Short strands of amino acids connected by peptide bonds are called peptidides. Proteins are long chains of amino acids. Oligopeptides, which comprise dipeptides, tripeptides, and tetrapeptides, are chains of fewer than twenty amino acids. A polypeptide is a peptide chain that is longer, continuous, and unbranched. Therefore, along with

nucleic acids, oligosaccharides, polysaccharides, and others, peptides belong to the large chemical families of biological polymers and oligomers. A protein is a polypeptide that has more than 50 amino acids, on average. A protein is made up of one or more polypeptides that are structured in a biologically useful manner. Proteins are frequently coupled to other proteins, other macromolecules like DNA or RNA, or complex macromolecular assemblies. Residues are amino acids that have been integrated into peptides. Each amide bond causes the release of a water molecule. All peptides have an N-terminal (amine group) and C-terminal (carboxyl group) residue at the end of the peptide, with the exception of cyclic peptides (Xia et al., 2004).

DISCUSSION

For the treatment of cancer, numerous biopharmaceuticals based on other non-IgG protein scaffolds have been created. Due to their tiny size, which is below the renal filtration threshold, the majority of these therapeutic proteins are rapidly removed from circulation, resulting in a short serum half-life. The short serum half-life of therapeutic proteins has been extended using a number of different techniques in order to prevent infusion or repeated injections of the proteins to maintain high serum concentrations. One such strategy is to grow the protein's hydrodynamic radius and corresponding size above the renal filtration threshold. The chemical conjugation of polymers, like polyethylene glycol, has been the most common (PEG).

However, batch-to-batch consistency and half-life optimization are challenging due to the high polydispersity of PEG molecules, which results in molecules with a wide size distribution. Additionally, PEG must be chemically conjugated to the therapeutic protein via designed reactive sites, adding extra stages to the product creation and analysis process and complicating repeatability. PEG is not biodegradable; it builds up in different tissues and can cause cellular and renal tubular vacuolation. Patients receiving PEGylated biopharmaceuticals have been found to develop neutralising anti-PEG antibodies, which can speed up the removal of PEG from the bloodstream (Price et al., 2002).

Exploiting the neonatal Fc receptor's built-in recycling mechanism by linking the therapeutic protein to serum albumin, serum albumin binding domains, or the Ig-Fc domain is another frequently utilised half-life extension technique. The endosomal FcRn-recycling process has been proven to be more efficient than just enlarging the protein and the effects of both strategies can be combined. On the other hand, this method cannot be used to modify a substance so that their intermediate pharmacokinetics is predictable. This might be advantageous for medicines with systemic toxicity, where it is necessary to strike a balance between off-target effects and targeted efficacy (Kutay et al., 2006).

CONCLUSION

Although many physiologically active proteins have short half-lives due to rapid renal elimination, therapeutic fusion proteins (TFPs) offer the benefit of half-life extension by the addition of an Fc binding moiety. We suggested a bioanalytical approach in this study to describe the plasma exposure and tumour distribution of TFPs. We proposed the method to characterise the pharmacokinetic properties of TFPs in the nonclinical in vivo study by specific LBA or IC-LC/MS to detect the entire TFP molecule including interferon alpha rather than the human IgG4 backbone of TFP because an IC-LC/MS assay with a generic human IgG4 signature peptide significantly underestimated the tumour distribution of TFP. Additionally, the modified minimum PBPK model with the addition of a tumour compartment provided clear definition of the link between observed plasma and tumour pharmacokinetics. For a more comprehensive knowledge of the pharmacokinetic profile of experimental TFPs in the biotherapeutic discovery process, the outlined tests and modelling studies may be helpful (Wei et al., 2017).

This demonstrates the broad range of functionalities that can be added to antibodies, antibody fragments, nanobodies, and other non-immunoglobulin scaffolds through direct genetic fusion or conjugation to recombinant protein polymers. Each biopolymer possesses properties that can help bring these protein therapies to the clinic, such as increased avidity, improved circulation half-life, or different purifying techniques. Several recombinant protein polymer conjugates to other classes of protein therapeutics have shown promising results in clinical trials, despite the fact that no clinical studies have used these biopolymers in combination with antibodies, antibody fragments, nanobodies, or non-immunoglobulin scaffolds to date. Additionally, the variety and continuous growth of protein biologics on the market will increase the need for cutting-edge drug delivery strategies. For instance, as antibody design and new linking chemistries advance, the proportion of combination products like antibodydrug conjugates (ADCs) will rise (Singh 1997). To maximise drug potency, avoid off-target toxicities, and enhance therapeutic index, these ADCs will need more sophisticated control over the drug delivery process. The development of new endosomal escape techniques has also increased the capacity for successful antibody delivery into the cellular cytoplasm. In the meantime, antibodies and antibody-like molecules offer new prospects for reaching intracellular "undruggable" targets. In order to improve the clinical potential of ADCs, intracellular antibodies, and other novel antibody products, protein polymers present a natural solution. Additionally, the presence of new regulatory frameworks will hasten the translational and commercialization processes. We conclude from these factors that recombinant protein polymers will become much more clinically relevant in the delivery of antibodies and antibodies-like binders in the near future. Protein polymers may be used to build and

modify hierarchical biomaterial structures, opening up new possibilities for antibody-protein polymer structures. This could lead to a novel ability to organise antibody or antibody-like domains into three-dimensional nano and microstructures that are important for drug delivery (Tian et al., 2010). The creation of hydrogel structures makes up a significant portion of the application space for elastin-like, silk-like, resilin-like, and collagen-like polypeptides and their hybrids. Some of these hydrogels have already been used for the sustained local delivery of antibodies. Furthermore, by utilising the strand invasion capability of CLPs for stable and controllable binding to denatured collagen, unique modes of hydrogel modification with growth factors, nanoparticles, and other drug delivery moieties are made possible by the inherent properties of protein polymers, such as synthetic collagen-like polypeptides. Covalent bonding between the CLP and ELP allows for temperature-responsive regulation of the nanoparticle assembly state and drug administration (Hamilton et al., 2002). The self-assembly characteristics of CLPs and ELPs have been coupled to construct vesicular nanoparticles from CLP-ELP fusions. Additionally, safe bioconjugation methods like sortase a ligation, SpyCatcher/SpyTag chemistries, and artificial amino click chemistries can be used to allow controlled decoration of hydrogels and nanostructures with antibodies or nanobodies without interfering with the assembling process. By enabling precise control of antibody presentation, organisation, and activity within the context of a wide array of advanced molecules, nanostructures, and biomaterials, the ability to utilise the diverse properties of protein polymers in conjunction with antibodies will greatly expand the variety of applications of antibody-protein polymer fusions. It has been demonstrated that additional recombinant technologies like Fc domain fusion and HSA-targeting offer some of the same benefits as recombinant protein polymers. These fusion partners are probably going to have an effect on each individual antibody's immunogenicity, solubility, aggregation behaviour, and dissociation constant. On a case-by-case basis, further preclinical studies that completely encompass these difficulties must be conducted.

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