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Biopharmaceuticals Nutrient Accumulation as well as Biocompatibility

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Introduction

Biopharmaceuticals rely heavily on recombinant proteins. The tendency of the active pharmaceutical ingredients to aggregate, resulting in irreversible drug loss and an increase in immunogenicity risk, is a significant challenge in the manufacturing and formulation of protein biologic products. While the molecular mechanisms of protein aggregation have been extensively discussed in the literature, knowledge gaps remain in connecting the phenomenon in the context of biotherapeutic immunogenicity. In this review, we discussed the factors that cause pharmaceutical recombinant protein aggregation and highlighted methods for prediction and mitigation that can be used throughout the development process, from formulation to bioproduction. The goal is to spark new conversations that will bridge the gap between physical characterizations of protein aggregates in biotherapeutics and functional properties of protein aggregates [1].

The rapid growth of biologic drugs in recent years has created an urgent need for early and precise control of product quality, with protein aggregation remaining a key challenge due to its implications in potency and safety. It is critical to understand the molecular mechanisms of protein aggregation in order to develop mitigation strategies. Proteins aggregate in three ways, each defined by the seeding entity: native monomers, denatured proteins, and pre-existing aggregates. Monomers of native proteins can self-assemble into oligomers via charge-charge interactions or covalent linkages formed between hydrophilic and hydrophobic residues on the protein's surface. Non-covalent oligomers with low molecular weights can revert to their native states, but as the oligomers grow in size, the associations become irreversible [2].

There are two types of aggregates: soluble and insoluble. Soluble aggregates are reversible and have a low molecular mass. A small amount of soluble aggregates, such as 5 to 10%, may be acceptable in biologic products because it is generally thought to be impractical to eliminate aggregates below these levels. Aggregates become irreversible and precipitate out of solution when protein aggregation exceeds the solution solubility limit. The amount of insoluble aggregates that can be tolerated appears to be related to the size of three particulates detected in the protein product upon reconstitution. Particles as small as 150 m in diameter can be detected visually in injectable products. Contrary to popular belief, particles smaller than 150 m are more likely to elicit immune responses.

Aside from aggregation mechanisms, solubility, and size, protein aggregation can be classified as intrinsic or extrinsic. Intrinsic protein aggregation occurs during the synthesis and purification steps of the protein formulation. Extrinsic aggregation, on the other hand, is caused by protein contacts with external sources during processing, such as glass surfaces inside containers, stainless steel of bioprocessing equipment, or silicon oil droplets inside pre-filled syringes. Because these two categories are intertwined and contribute collectively to protein aggregates detected downstream, specific attribution to each is frequently avoided. In this review, we will concentrate on intrinsic protein aggregation, which can be predicted and mitigated as early as the drug development process.The main points and motivations of our discussion have been summarized [3].

Protein aggregation is assessed by looking at conformational and colloidal stability. Proteins are motivated by thermodynamics to maintain their native conformations at the lowest energy level possible in order to achieve high stability. In hydrated environments, hydrophobic amino acid residues prefer to be in the core, while hydrophilic residues prefer to be in the outer shell. Water molecules tend to organise into loose structures around the hydrophobic moieties, so not all apolar residues are completely buried in the interior. The entropy of the system increases as structured water is released into the bulk solvent as a result of protein folding, surface adsorption, or the collapse of hydrophobic patches. The increase in entropic cost, combined with a decrease in enthalpy due to bond formations among amino residues, reduces the system's Gibb's free energy.

Immunogenicity is defined as a protein biotherapeutic's proclivity to elicit undesirable harmful immune responses against itself for the purposes of this review. Because of the way biologics have historically been synthesised, species difference is frequently regarded as the primary cause of immunogenicity. Recombinant technology has advanced over the last two decades to the point where many recently approved monoclonal antibodies are "humanised" or "fully human," with the latter developed using libraries of human immunoglobulin sequences. Nonetheless, research has shown that even human-like antibodies can induce anti-drug antibodies. Most likely, these biologics do not elicit immune responses via xenogeneic epitope recognition by human B and T cell repertoires. As a result, protein aggregation has been proposed as a drug-intrinsic factor in the formation of ADA [4].

Description

Protein aggregation, ADAs, and immunogenicity have all been studied extensively in vitro, in vivo, and clinical studies. The majority of in vitro mechanistic studies use a traditional experimental design in which protein aggregation is induced under accelerated and exaggerated stress conditions before being exposed to selected immune cells. RombachRiegraf et al. used shear stress, heat, shaking, and freeze-thaw cycles to induce subvisible aggregation in antibodies in order to study the effects of these aggregates on activating dendritic cells (DCs) in vitro. As the most potent APCs, DCs are thought to play a key role in CD4+ T cell activation and polarisation, which can influence the immunogenicity of a given therapeutic antibody. Prior to human trials, animal models are required to assess the immunogenicity of candidate protein drugs. Kijanka et al. investigated the effect of murine mAb aggregate size on BALB/c mice subcutaneous injection. Low pH and high temperatures were used to induce aggregates at three different sizes: soluble oligomers, submicron particles, and micron particles. The mice developed measurable ADAs in serum, possibly due to enhanced DCs uptake, in the submicron size group, which was rated as the most immunogenic. In this mouse model, samples enriched in soluble oligomers and micron size particles did not cause significant ADA [5].

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Conclusion

To improve the translational relevance of in vivo immunogenicity data, transgenic mouse models have been developed. According to Van Beers et al., aggregates of a recombinant human interferon beta formulation elicit neutralising ADAs in wild-type mice but not in transgenic mice expressing a mini-repertoire of human IgG1 antibodies, highlighting the importance of humanised mouse models in immunogenicity prediction. ADAs were produced by Bessa only soluble human mAb covalent aggregates with a high degree of neoepitopes (generated by chemical modifications). Non-covalent aggregates, on the other hand, did not elicit immunogenicity in the same model. While transgenic models appear to be superior to wild-type animals in predicting immunogenicity in humans, the reliability is likely to be highly dependent on the specific drugs and the nature of the aggregates tested.

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Conflict of Interest

There are no conflicts of interest by author.

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