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Protein Therapeutic Immunization and Computational Epitope Identification

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Editorial

Biotherapeutics and antimicrobial proteins in particular, are of increasing interest for human medicine. An important challenge in the development of such therapeutics is their potential immunogenicity, which can induce production of anti-drug-antibodies, resulting in altered pharmacokinetics, reduced efficacy, and potentially severe anaphylactic or hypersensitivity reactions. For this reason, the development and application of effective deimmunization methods for protein drugs is of utmost importance. Deimmunization may be achieved by unspecific shielding approaches, which include PEGylation, fusion to polypeptides reductive methylation, glycosylation, and polysialylation. Alternatively, the identification of epitopes for T cells or B cells and their subsequent deletion through site-directed mutagenesis represent promising deimmunization strategies and can be accomplished through either experimental or computational approaches. This review highlights the most recent advances and current challenges in the deimmunization of protein therapeutics, with a special focus on computational epitope prediction and deletion tools [1,2].

The immune systems of humans and other mammals evolved to defend them from pathogenic microbes, invading viruses or other substances that are not beneficial or may cause harm. Additionally, the immune system has the ability to discriminate self from non-self. Also, tolerance of commensal organisms, indispensable for our body, is an essential competence of the immune system. In order to use proteins, including enzymes, as therapeutic agents to tackle complex and persistent diseases, it is necessary to avoid a strong immune response to these agents as a result of the treatment. Systemic application of therapeutic proteins could not only lead to unpredictable pharmacokinetics (PK) and pharmacodynamics (PD) due to an immune response, the induction of anti-drug antibodies (ADAs) and loss of efficacy, but also to anaphylactic responses, hypersensitivity, and other complications. The immune system can be divided into the innate and adaptive immune system. Components of both systems interact and play important roles in an immune response. The innate immune response describes an unspecific defence mechanism, which is germ-line encoded and includes physical barriers, soluble proteins as well as cellular components such as phagocytes and natural killer cells. In contrast, the adaptive immune response is characterized by its high specificity for target antigens.

The efficient DE immunization of bio therapeutics is of increasing interest in human medicine. The design and production of protein-based vaccines or enzyme-based antimicrobials are just a few examples of the diversity of applications that can profit from targeted deimmunization. The process of protein deimmunization can be divided into several steps, i.e., epitope prediction, epitope identification and epitope deletion, each of them holding their own complexities and challenges. Not only can epitope identification and prediction be useful to solve biomedical questions, but they could also shed light on immunological processes in general or be used for the prediction of epitopes in the diagnosis of disease. One trend common to all three steps of protein deimmunization is the desired and often successful transition from experimental to computational methods. Even though shielding methods have been proven to be an efficient tool to deimmunize peptides or proteins, they are possibly not the best choice for biotherapeutics with enzymatic activity due to the possible masking of the active sites. Instead, the alteration and deletion of predicted and identified epitopes on biotherapeutic drugs through exchange of amino acids appears to be a more promising approach, particularly when efficient computational tools are available.

The implementation of machine learning techniques in the field of immunoinformatics for epitope prediction underpins the complexity of these processes. The problem is further complicated by the enormous diversity of the HLA alleles in humans and the resulting variety of epitopes that can possibly be identified by the immune systems of different patients. In order to produce deimmunized biotherapeutic drugs effective in all patients, all these different alleles would need to be considered. In this context, an interesting option may be the development of personalized deimmunized biotherapeutics, taking into consideration only individual HLA alleles. These personalized deimmunized drugs, however, would generate high costs for patients and/or healthcare systems (even though the use of computationally-driven methods can reduce costs for drug development significantly) and likely face regulatory obstacles. In general, computationally-driven methods for epitope prediction depend on the quality of the input data that are provided, the degrees of freedom allowed, and the algorithms used. Nevertheless, computational methods have already been reported to be more accurate than experimental approaches in epitope prediction in some cases, e.g., for the development of peptide-based vaccines [3-5].

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