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REVIEW

T-cell dependent immunogenicity of protein therapeutics: Preclinical assessment and mitigation

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Abstract Protein therapeutics hold a prominent and rapidly expanding place among medicinal products. Purified blood products, recombinant cytokines, growth factors, enzyme replacement factors, monoclonal antibodies, fusion proteins, and chimeric fusion proteins are all examples of therapeutic proteins that have been developed in the past few decades and approved for use in the treatment of human disease. Despite early belief that the fully human nature of these proteins would represent a significant advantage, adverse effects associated with immune responses to some biologic therapies have become a topic of some concern. As a result, drug developers are devising strategies to assess immune responses to protein therapeutics during both the preclinical and the clinical phases of development. While there are many factors that contribute to protein immunogenicity, T cell- (thymus-) dependent (Td) responses appear to play a critical role in the development of antibody responses to biologic therapeutics. A range of methodologies to predict and measure Td immune responses to protein drugs has been developed. This review will focus on the Td contribution to immunogenicity, summarizing

Abbreviations: Td, T-cell dependent, thymus dependent; T, thymus; ADA, anti-drug antibodies; Ti, T-cell independent; APC, antigen-presenting cells; HLA, human leukocyte antigen; MHC, major histocompatibility complex; TCR, T cell receptor; Treg, regulatory T cells; FVIII, factor VIII; nTregs, natural regulatory T cells; aTreg, adaptive regulatory T cells; iTreg, induced regulatory T cells; IEDB, Immune Epitope Database Analysis Resource; IC_{50}, 50% inhibitory concentration; ELISpot, enzyme-linked immunosorbent spot-forming; ELISA, enzyme-linked immunosorbent assay; CFSE, carboxyfluorescein succinimidyl ester; PBMC, peripheral blood mononuclear cells; ALN, artificial lymph node; ORG, unmodified original epitopes; FPX, recombinant Fc fusion protein; SFC, spot-forming cells.

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current approaches for the prediction and measurement of T cell-dependent immune responses to protein biologics, discussing the advantages and limitations of these technologies, and suggesting a practical approach for assessing and mitigating Td immunogenicity.
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1. Introduction

1.1. The immunogenicity of protein therapeutics

Since the approval of the first recombinant biological therapeutic, insulin, in October 1982, more than 165 biotherapeutic agents have entered the marketplace and have generated an estimated $99 billion in sales worldwide [1–4]. Therapeutic biologics offer the advantages of increased specificity and reduced toxicity compared to small molecules. However, when administered to patients, these protein-based drugs have the potential to elicit immune responses that may directly impact drug safety, efficacy, and potency. For example, anti-drug

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