Clinical Immunology

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1. Most Downloaded

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 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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2.Recent Articles

Maternal T and B cell engraftment in two cases of X-linked severe combined immunodeficiency with IgG1 gammopathy

Abstract

X-linked severe combined immunodeficiency (X-SCID), caused by defects in the common gamma chain, is typically characterized by T and NK cell defects with the presence of B cells. T cell dysfunction and impaired class-switch recombination of B cells mean that patients typically have defects in class-switched immunoglobulins (IgG, IgA, and IgE) with detectable IgM. Here, we describe two patients with X-SCID with IgG1 gammopathy, in whom we identified maternal T and B cell engraftment. Exclusively, maternal B cells were found among the IgD^{-} $CD27^{+}$ class-switched memory B cells, whereas the patients' B cells remained naïve. *In vitro* stimulation with CD40L + IL-21 revealed that peripheral blood cells from both patients produced only IgG1. Class-switched maternal B cells had restricted receptor repertoires with various constant regions and few somatic hypermutations. In conclusion, engrafted maternal B cells underwent class-switch recombination and produced immunoglobulin, causing hypergammaglobulinemia in patients with X-SCID.

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3.Most Cited

Immunopathogenesis of osteoarthritis

Abstract

Even though osteoarthritis (OA) is mainly considered as a degradative condition of the articular cartilage, there is increasing body of data demonstrating the involvement of all branches of the immune system. Genetic, metabolic or mechanical factors cause an initial injury to the cartilage resulting in release of several cartilage specific auto-antigens, which trigger the activation of immune response. Immune cells including T cells, B cells and macrophages infiltrate the joint tissues, cytokines and chemokines are released from different kinds of cells present in the joint, complement system is activated, and cartilage degrading factors such as matrix metalloproteinases (MMPs) and prostaglandin E_2 (PGE_2) are released, resulting in

further damage to the articular cartilage. There is considerable success in the treatment of rheumatoid arthritis using anti-cytokine therapies. In OA, however, these therapies did not show much effect, highlighting more complex nature of pathogenesis of OA. This needs the development of more novel approaches to treat OA, which may include therapies that act on multiple targets. Plant natural products have this kind of property and may be considered for future drug development efforts. Here we reviewed the studies implicating different components of the immune system in the pathogenesis of OA.

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4. Open Access Articles

مقاله های زیر بصورت کامل قابل دریافت و درصورت تمایل قابل ترجمه می باشند

High resolution IgH repertoire analysis reveals fetal liver as the likely origin of life-long, innate B lymphopoiesis in humans

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Abstract

The ontogeny of the natural, public IgM repertoire remains incompletely explored. Here, high-resolution immunogenetic analysis of B cells from (unrelated) fetal, child, and adult samples, shows that although fetal liver (FL) and bone marrow (FBM) IgM repertoires are equally diversified, FL is the main source of IgM natural immunity during the 2nd trimester. Strikingly, 0.25% of all prenatal clonotypes, comprising 18.7% of the expressed repertoire, are shared with the postnatal samples, consistent with persisting fetal IgM + B cells being a source of natural IgM repertoire in adult life. Further, the origins of specific stereotypic IgM + B cell receptors associated with chronic lymphocytic leukemia, can be traced back to fetal B cell lymphopoiesis, suggesting that persisting fetal B cells can be subject to malignant transformation late in life. Overall, these novel data provide unique insights into the ontogeny of physiological and malignant B lymphopoiesis that spans the human lifetime.

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