MULTI-EPITOPE CITRULLINATED PEPTIDE FOR TREATMENT OF RHEUMATOID ARTHRITIS (Tel Hashomer)
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Multi-Epitope Citrullinated peptide for treatment of Rheumatoid Arthritis

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Abstract

Citrullinated peptides are major targets of disease-specific autoantibodies in Rheumatoid Arthritis (RA). The formation of citrullinated peptideselicits an immune response that lead to tolerance breakdown manifested by production of anti-citrullinated protein antibodies (ACPA). Currently, citrullinated peptides serve as a biomarker for the diagnosis of RA by measuring ACPA titers in patient's sera. The accumulations of citrullinated proteins at inflammation sites suggest them as targets for tolerance induction. Since a diversity of citrullinated autoantigens exist in RA we tailored a multi-epitope citrullinated peptide (Cit-ME), derived from sequence of the most prevalent citrullinated autoantigens. The ability of the Cit-ME peptide to induce tolerance following administration to arthritic rats was studied. Treatment of Adjuvant Induced Arthritis with Cit-ME reduced significantly the disease severity compared to untreated rats.
Moreover, amelioration of disease manifestations was shown by increased regulatory T cells and apoptosis rate and reduced Th17 cells.

We also found that RA-patient's derived PBMC incubated in the presence of Cit-ME peptide elicited up-regulation of the TGF- gene expression that was associated with an increase in $CD4^{+}FoxP3^{+}$ T regulatory cell and elevated T cells apoptosis rate. In addition it reduced the expression of the pathogenic cytokines INF- and TNF- and the proportion of Th-17 cells.Thus, the use of citrullinated peptides-based immunotherapy may be a promising approach for tolerance induction in experimental arthritis and perhaps even in susceptible individuals that are ACPA seropositive in human arthritis.

Moreover,immunotherapy based on citrullinated peptides could be given as preventive treatment to susceptible ACPA+ population as personalized medicine

prior to disease onset. In an attempt to develop a preventive treatment given to delay or prevent arthritis symptoms onset in susceptible ACPA sero-positive individuals prior to arthritis course.

The Need

Currently, citrullinated peptides serve as a biomarker to identify ACPA presence and titers in patient's sera. Our innovative approach is to employ the citrullinated peptides as immune tolerance inducing agents that will assist to reverse the abnormal immune response in RA. To the best of our knowledge this study is the first to employ citrullinated peptides as tolerogenic agents for immunomodulation and restoration of the autoimmune response in RA.

Applications

The aim of this study is to elucidate essential mechanisms of immune tolerance induction with citrullinated peptides. Successful achievement of our tasks will provide a new horizon for future development of immune therapy based on citrullinated peptides to suppress the autoimmune response in arthritis. The advantages of tolerance induction-based approach over other general immune modulating therapies, relies in its effective suppression of the specific-autoreactive immune responses, without widely affecting the entire immune system as most available treatments do.

The citrullinated peptides used in this study derived from endogenous protein sequences expressed exclusively in diseased targeted tissues in arthritic state and not in healthy tissues.

In addition the advantage of administration of a multi-epitope peptide over whole protein is less susceptibility to produce autoantibodies against a peptide due to their relatively low molecular weight.

Advantages

Our innovative approach is to employ the citrullinated peptides as tolerance inducing agents that will assist to restore the abnormal immune response in RA. To the best of our knowledge this study is the first to employ citrullinated peptides as tolerogenic agents for immunomodulation and restoration of the autoimmune response in RA.

Future development of immunotherapy based on immune tolerance based on citrullinated could be given to prevent or delay arthritis onset to susceptible subpopulation diagnosed as ACPA sero-positive individuals prior to arthritis symptoms that could develop arthritis in the near future.

The Market

The prevalence of RA is estimated to be 0.8% worldwide, with women twice as

likely to develop the disease as men. In the United States, RA afflicts 1.3 million people with a further 126,000 new diagnoses each year. It is responsible for 250,000 hospitalizations and 9 million physician visits each year. According to Global Data, the RA therapeutics market was valued at $10.3 billion globally in 2010, and has doubled over a four-year period after growing at a Compound Annual Growth Rate (CAGR) of 12.3%[2]. More than 80% of drug sales are biological agents although these are more often used as second line therapy due to their high cost.

Drugs used for treatment of RA are classified as first line agents- consisting of non steroidal anti-inflammatory drugs (NSAIDs) and steroids such as glucocorticoids and second line agents- consisting of disease modifying anti-rheumatic drugs such as chloroquine, gold salts, penicillamine, cyclosporine, and several biological agents like TNF- and interleukin-1 inhibitors.

Global rheumatoid arthritis market is driven by increase in incidences of RA patients, global ageing population and increasing healthcare expenditure by government of various nations. Factors which are affecting pharmaceutical companies are pricing pressure, patent expiries of RA drugs, high costs of treatments involved and escalating R&D costs.

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