Anti-coll-II

Anti-Citrullinated Protein Antibodies as Novel Therapeutic Drugs in Rheumatoid Arthritis

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ABSTRACT

We have developed a novel antibody-based treatment for rheumatoid arthritis, in a collagen antibody-induced arthritis mouse model, anti-citrullinated protein antibodies (ACPAs) prevent the onset and/or exacerbated of inflammation, and prevent or strongly reduce joint damage. For the development of this novel therapy, we focused on rheumatoid arthritis-specific citrullinated peptide epitopes. A growing number of studies indicate that modifications of arginines into citrulline residues are responsible for the initial triggering of autoimmunity and the breaking of tolerance. We identified a subset of human recombinant ACAAs that prevent the onset of inflammation in both collagen-induced arthritis and collagen antibody-induced arthritis mouse models for rheumatoid arthritis. Therapeutic administration of these antibodies resulted in the arrest of the inflammation and prevented a further increase of the inflammatory response. Prophylactic administration significantly prevented the onset of inflammation. Histological analysis of inflamed joints from ACPA treated mice revealed a significant decrease in joint damage, as compared to control animals. To identify the differentiating therapeutic epitope recognized by the therapeutic ACAAs (tACPA), we performed comparative immunoprecipitations with therapeutic and non-therapeutic ACPAs using human PAD4-deiminated HEK293 cell lysates, followed by mass spectrometry analysis. The differentiating peptide epitope that is recognized by tACPA, we performed comparative immunoprecipitations with therapeutic and non-therapeutic ACPAs using human PAD4-deiminated HEK293 cell lysates, followed by mass spectrometry analysis. The differentiating peptide epitope that is recognized by tACPA was identified as lead distinguishing epitope for therapeutic versus non-therapeutic antibodies. The second generation of antibodies was selected against this domain by means of phage display and by hybridoma generation. The second generation of antibodies was compared of even more potent inhibitors of the inflammatory response. Here, we describe the identification of a series of antibodies directed against a citrullinated epitope present in murine and human histone-2A. In mouse inflammatory response. Here, we describe the identification of a series of antibodies directed against a citrullinated epitope present in murine and human histone-2A. In mouse models for rheumatoid arthritis we demonstrate that these tACPA exhibit a strong anti-inflammatory activity and prevent the occurrence of swelling and joint damage. We propose anti-histone-2A ACPA as a novel therapeutic treatment for rheumatoid arthritis patients.

1st generation anti-cit hMabs in CAIA

Therapeutic RhmAb2.102 treatment

Histological analysis of RhmAb2.102 treated CAIA joints

Target validation

IP of RhmAb2.102 on PAD citrullinated HEK293 lysates

Conclusions

ModiQuest has developed a family of novel rCit-hMabs which have strong therapeutic potential in regard to preventing: 1) the onset of the inflammation, 2) joint damage during inflammation, 3) further increase of inflammation and swelling, 4) inflammation relapse and tissue/joint damage to occur.

The availability of the previously developed diagnostic test for RA, detecting RA up to 10 years before onset of the disease (Immunoscan, Euro-diagnostica AB; DiastatTM, Axis-Shield), makes this novel therapeutic approach of special interest for early stage RA. In a more progressive form of RA a combination therapy might be possible with existing biologicals that have different mechanisms of action.

References

van Venrooij et al. Ann NY Acad Sci 2008; 1143:p268