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Anti-citrullinated protein antibodies as novel therapeutic drugs in rheumatoid arthritis

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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 exacerbation of inflammation, and prevent or strongly reduce joint damage. For the development of this novel therapy, we focussed 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 ACPAs 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 ACPA (tACPA), we performed comparative immunoprecipitations with therapeutic and non-therapeutic ACPAs using human PAD4-deiminated HEK-293 cell lysates, followed by mass spectrometry analysis. The differentiating peptide epitope that is recognized by tACPAs only, is a citrullinated domain of Histone-2A. A second generation of antibodies was selected against this domain by means of phage display and by hybridoma generation. The second generation of tACPAs was comprised 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 models for rheumatoid arthritis we demonstrate that these tACPAs exhibit a strong anti-inflammatory activity and prevent the occurrence of swelling and joint damage. We propose anti-histone-2A tACPA as a novel therapeutic treatment for rheumatoid arthritis patients.

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