Identification of citrullination sites specific for peptidylarginine deiminase 2 (PAD2) and PAD4 in fibrinogen from synovial fluid of patients with rheumatoid arthritis

Background: Protein citrullination, i.e. conversion of arginine residues into citrulline residues, is a post-translational modification catalyzed by PAD, and is an important pathophysiological determinant in conditions such as Rheumatoid arthritis (RA). Identification of citrullination sites on putative autoantigens is likely to enhance our understanding of PAD's substrate specificity. Objectives: Citrullinated fibrinogen is an autoantigen linked to the pathophysiology of RA. We have applied a novel MS-based proteomics approach to estimate the degree of citrullination in synovial fluid (SF) from RA patients, and compare to fibrinogen citrullinated in vitro by PAD2/4, the most important PAD isoforms involved in RA. The estimated degree of citrullination induced by the two isoforms is also compared to evaluate their relative impact. Methods: Fibrinogen was citrullinated in vitro by PAD2/4 and citrullination sites were identified by LC-MS/MS on a Q-exactive orbitrap following proteolytic digestion with Lys-C. These in vitro citrullination profiles were compared to those observed in SF fibrinogen of four RA patients with varying DAS28 scores, CRP levels and leukocyte counts. DAS28 scores >5.1 and ≤2.4 correspond to moderate to severe and low activity of disease, respectively. Patients with high inflammatory activity gave high CRP level and leukocyte count values. Results: A total of 52 citrullination sites were identified. Overall, PAD2 generated higher number of identified sites and higher degree of citrulline occupancy at given sites than PAD4. In fibrinogen from SF, 38 citrullination sites were identified, of which 23 have not been previously reported. Several of these sites were identified in more than one patient, and were regarded as hotspots. Fibrinogen from patients with high DAS28 levels contained markedly more citrullination sites and higher citrulline occupancy. Conclusions: Study suggests that PAD2 citrullinates fibrinogen more efficiently than PAD4 and citrullination of certain sites in fibrinogen from SF reflects disease activity. Identification of such sites may have diagnostic or prognostic value in RA and other inflammatory disorders.

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