Poster Presentation

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A molecular basis for citrullination dependent rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease, characterized by inflammation of synovial tissue, joint pannus and bone erosion. The human leukocyte antigen (HLA) locus plays a vital role in immunity, encoding highly polymorphic molecules that present peptides to T cell lymphocytes. RA has a strong association with a region of the HLA-DRB1 locus known as the 'shared epitope' (SE) and the presence of autoantibodies specific for citrullinated proteins. The SE maps to a highly polymorphic N-terminal region of the HLA-DRβ chain around amino acids 70-74. This region encodes a positively charged residue at position 71 that is thought to dictate the amino acid that is accommodated in the P4 pocket of the antigen-binding groove. Citrullination, the conversion of positively charged arginine to polar citrulline, is a physiological process catalyzed by peptidyl arginine deiminase. Previous studies have shown that citrullination of self-antigens can significantly increase the affinity of epitopes for SE alleles. Here we provide a molecular basis for how citrullinated vimentin and aggrecan epitopes can be presented by the SE alleles, HLA-DRB1*0401 and HLA-DRB1*0404. Citrulline was accommodated in the electropositive P4 pocket of HLA-DRB1*0401/04, whilst arginine was not. In addition, the RA resistant HLA-DRB1*0402 allomorph was capable of binding both arginine and citrulline in its electronegative P4 pocket. Peptide elution studies revealed that arginine was presented by HLA-DRB1*0402 but not by HLA-DRB1*0401/04. Moreover, citrullinated vimentin showed a greater sensitivity to proteolysis by cathepsin L, when compared to unmodified vimentin, indicating that citrullination can impact the repertoire of self-antigens presented. Using HLA Class II tetramers, we identified citrullinated vimentin and aggrecan specific CD4+ T cells from both HLA-DRB1*0401+ RA patients and healthy controls. In RA patients, the number of autoreactive T cells correlated with disease activity and were deficient in regulatory T cells compared to healthy controls. Together these findings provide significant insight into the role citrullination plays in the pathogenesis of RA[1].

[1] *S. Scally et al, J Exp Med, 2013, 210, 2569-82.*

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