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Title

Post-translational modifications of the extracellular matrix: key events in disease pathogenesis

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Introduction

The extracellular matrix (ECM) is both complex and dynamic; its composition and structure vary from one tissue to the next, and it is profoundly altered during disease. One key factor defining ECM content is post-translational modification of its protein constituents. However, surprisingly little is known about how the matrix is modified, and how this impacts ECM function. Citrullination, the conversion of the amino acid arginine to citrulline, is significantly elevated at sites of inflammation. My work investigates how citrullination of ECM proteins shapes innate and adaptive immune responses, and how these processes contribute to pathological autoimmunity in rheumatoid arthritis (RA).

Materials and Methods & Results

Distinct citrullinated sites on the matrix molecule tenascin-C were defined by mass spectrometry, and the functional consequences of these modifications on immune cell behaviour investigated. Citrullinated tenascin-C provoked elevated innate immune responses, creating a mobile, aggressive macrophage phenotype, by reducing cell adhesion and enhancing release of a unique signature of pro-inflammatory cytokines. Peptide mapping and protein mutagenesis identified the epitope within tenascin-C responsible for these effects. Targeted inhibition of inflammatory signalling pathways revealed a complex interplay between the immune sensor toll-like receptor 4 and macrophage integrins that is essential for the resolution of inflammation, but which citrullinated tenascin-C escapes, due to the loss of key arginines in integrin binding sites.

I also defined different citrullinated sites on tenascin-C that activate adaptive immunity in people with RA. These epitopes were capable of breaking immune tolerance, generating citrulline-specific pathogenic autoantibodies that are the hallmark of RA. Autoantibody responses towards one immunodominant epitope were examined in large patient cohorts and found to be an accurate means by which to diagnose established RA, as well as identifying people at risk of developing disease, years before the detection of clinical symptoms.

Discussion

My data demonstrate that ECM post-translational modification drives aberrant inflammation via multiple mechanisms; through breaking immune tolerance and the formation of pathogenic autoantibodies, and by activating innate pathways in manner that is no longer subject to homeostatic control. Understanding more about matrix modification therefore can provide novel approaches to disease diagnosis and treatment.