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Is the generation of neo-antigenic determinants by free radicals central to the development of autoimmune rheumatoid disease?

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Abstract

Biomolecules are susceptible to many different post-translational modifications that have important effects on their function and stability, including glycosylation, glycation, phosphorylation and oxidation chemistries. Specific conversion of aspartic acid to its isoaspartyl derivative or arginine to citrulline leads to autoantibody production in models of rheumatoid disease, and ensuing autoantibodies cross-react with native antigens. Autoimmune conditions associate with increased activation of immune effector cells and production of free radical species via NADPH oxidases and nitric oxide synthases. Generation of neo-antigenic determinants by reactive oxygen and nitrogen species ROS and RNS) may contribute to epitope spreading in autoimmunity. The oxidation of amino acids by peroxynitrite, hypochlorous acid and other reactive oxygen species (ROS) increases the antigenicity of DNA, LDL and IgG, generating ligands for which autoantibodies show higher avidity. This review focuses on the evidence for ROS and RNS in promoting the autoimmune responses observed in diseases rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It considers the evidence for ROS/RNS-induced antigenicity arising as a consequence of failure to remove or repair ROS/RNS damaged biomolecules and suggests that an associated defect, probably in T cell signal processing or/or antigen presentation, is required for the development of disease.
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Keywords: Reactive oxygen species; Reactive nitrogen species; Protein oxidation; Autoantigen; Neo-antigenic determinant; DNA oxidation

Contents

The phenotype of diffuse autoimmune diseases can be attributed, at least in part, to the abnormalities of the T cell population with an increased prevalence of $CD4^{+}CD28^{null}$ T cells which are neither anergic nor functionally paralyzed [1]. These cells have gained proinflammatory capacities and cytotoxic function and are resistant to apoptosis; T cell dysfunction is further

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confounded in autoimmunity by the presence of persistent immune complexes arising from the failure of effective antigen removal. Subsequent interaction with antibody results in immune complex formation and in turn the complexes bind phagocytic cells via Fcγ receptors to facilitate their clearance. Receptor engagement triggers a cascade of intracellular pathways in effector cells resulting in the production of free radicals by the NADPH oxidase on infiltrating neutrophils, monocyte/macrophages and resident tissue macrophages with concomitant activation of NFkB and pro-inflammatory gene expression [2]. The formation of high levels of the nitrogen-centred free radical, nitric oxide, in macrophages via iNOS in humans is debated although recent evidence from SLE patients suggests increased nitrite production associated with inflammation [3]. The release of myeloperoxidase from neutrophilic granules following activation by immune complexes also contributes to the oxidative environment in autoimmune disease [4]. Whilst low levels of oxidants have important roles as signalling molecules, over-production in the absence of adequate antioxidant defence may cause irreversible changes to biomolecules and contribute to disease progression.

Rheumatoid arthritis (RA) has a prevalence of 1:3 of the over-65 population of developed countries, with both systemic and localised (within articular joints) components. The rheumatoid joint is recognised as a site which undergoes repetitive cycles of ischemia and reperfusion and formation of oxygen-derived free radicals [5] with the gene expression profile varying according to the degree of hypoxia and re-oxygenation. The autoimmune disease, systemic lupus erythematosus (SLE), has a strong inflammatory component, which is typified by chronic over-production of ROS and RNS [6].

This review focuses on the current knowledge of the differential roles of acute and chronic ROS and RNS production in the generation of neo-antigenic determinants which may serve as drivers of T and/or B cell activation with particular focus on SLE and RA.

1. Generation of neo-antigenic determinants

Why antigens which have previously been tolerated may later be seen as foreign is the subject of several hypotheses; molecular mimicry has recently been reviewed by Blank [7] and is based on the concept that viral or bacterial antigens serve as antigenic mimics, i.e., identical to a self protein and, although a normal immune response is developed to the pathogen, the resultant antibodies show cross-reactivity towards self-antigen.

More recently, epitope spreading has gained credence as a major driver underlying autoimmunity (Fig. 1). This hypothesis suggests that the development of antibodies against other cryptic epitopes on the original antigen, after self-tolerance has been broken, provides a mechanism for the development of autoantibody production in a

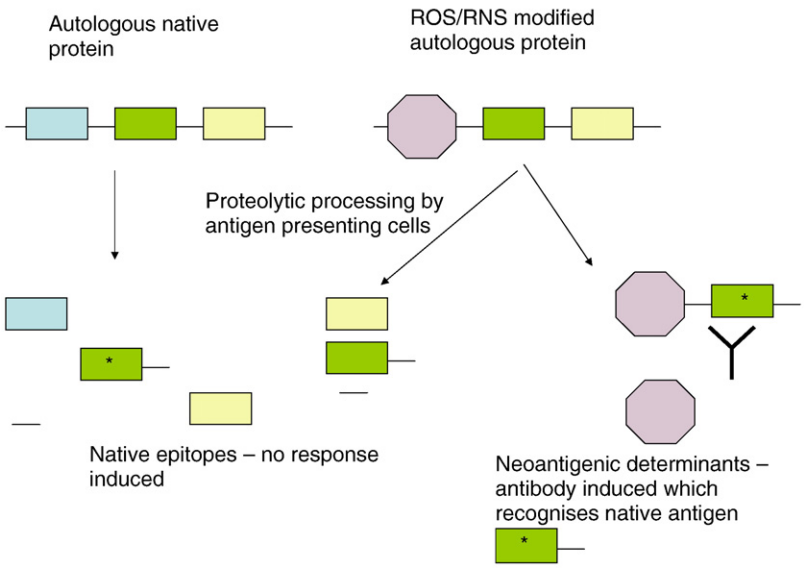

Fig. 1. Neo-antigenic determinant-driven antibody response. Native peptides do not trigger immune responses. Modification of amino acids by reactive oxygen species (ROS) or reactive nitrogen species (RNS) may alter proteolytic processing revealing new epitopes which are immunogenic. Antibodies reactive with neo-antigenic determinants may subsequently cross-react with native antigens in a process known as epitope spreading.

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