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Review

Evolutionarily conserved antigens in autoimmune disease: Implications for an infective aetiology

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ABSTRACT

The immune system has evolved to eliminate or inactivate infectious organisms. An inappropriate response against self-components (autoantigens) can result in autoimmune disease. Here we examine the hypothesis that some evolutionarily conserved proteins, present in pathogenic and commensal organisms and their hosts, provide the stimulus that initiates autoimmune disease in susceptible individuals. We focus on seven autoantigens, of which at least four, glutamate decarboxylase, pyruvate dehydrogenase, histidyl-tRNA synthetase and alpha enolase, have orthologs in bacteria. Citrullinated alpha-enolase, a target for autoantibodies in 40% of patients with rheumatoid arthritis, is our main example. The major epitope is highly conserved, with over 90% identity to human in some bacteria. We propose that this reactivity of autoantibodies to shared sequences provides a model of autoimmunity in rheumatoid arthritis, which may well extend to other autoimmune disease in humans.

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1. Introduction

The adaptive immune system provides an important line of defence against infectious agents and has evolved an array of tolerance mechanisms, which prevent inappropriate responses against self-(auto) antigens. Because the discrimination between self- and nonself-reactive lymphocytes is imperfect, some self-reactive lymphocytes may mature and, in the presence of danger signals from the innate immune system, become activated and cause autoimmune disease.

Autoimmune diseases are increasingly diagnosed by their associated autoantibodies. Traditionally, such antibodies are detected with immunological assays such as indirect immunofluorescence, which define antibodies targeting tissues including the thyroid, pancreas and gastric parietal cells. Using cell lines, antibodies to subcellular components, for example nuclei, nucleoli, ribosomes and mitochondria, can also be identified. The need for more disease-specific tests has driven the search for the actual molecules that are targeted by these antibodies, and has resulted in the dis-

Abbreviations: ANCA, anti-neutrophil cytoplasmic antigens; 2-OADC, 2-oxo-acid dehydrogenase complex; BLAST, basic local alignment search tool; CCP, cyclic citrullinated peptide; GABA, γ-aminobutyric acid; GAD, glutamate decarboxylase; HisRS, histidyl-tRNA synthetase; LPS, lipopolysaccharide; MS, multiple sclerosis; PAD, peptidyl arginine deiminase; PDC-E2, pyruvate dehydrogenase complex E2 component; PR3, proteinase 3; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

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Table 1
Organ-specific and non-organ-specific autoimmune diseases and their antigens.

	Disease	Generic autoantibody target	Specific autoantigen(s)	Bacterial orthologs	Reference
Organ specific	Hashimoto's thyroiditis	Thyrocyte	Thyroid peroxidase	?+	Daiyasu and Toh, 2000
	Grave's disease	Thyrocyte	Thyrotropin receptor		
	Type I diabetes mellitus	Pancreatic islet cell	Glutamic acid decarboxylase 65	+	García and López, 1995 Ueno, 2000
	Celiac disease	Endomyceal	Tissue transglutaminase		
	Autoimmune gastritis	Gastric parietal cell	Intrinsic factor		
	Myasthenia gravis	Acetylcholine receptor	Acetylcholine receptor	+	Bocquet et al., 2007[1] Hilf and Dutzler, 2008[2]
	Neuromyelitis optica (Devic's disease)	NMO IgG	Aquaporin-4	+	Calamita et al., 1995[3]
	Autoimmune haemolytic anaemia	Erythrocyte	various cell surface glycoproteins		
	Primary biliary cirrhosis	Mitochondria	Pyruvate dehydrogenase complex E2	+	Selmi et al, 2003
	Addison's diseae	Adrenal Cortex	21 hydroxylase		
	Goodpastures syndrome	Glomerular basement membrane	Type IV collagen		
	Sjogren's syndrome	Ro, La	Ro/SSA, La/SSB		
	Polymyositis	Jo-1 (and others)	Histidyl tRNA synthetase	+	Raben et al., 1994
	Rheumatoid Arthritis	Citrullinated (cit) proteins	(cit)fibrin, (cit)vimentin, (cit)collagen, (cit)α-enolase	+	Pancholi, 2001
	Systemic sclerosis	DNA binding proteins	Topoisomerase-1 Centromeric proteins A & B	+	Forterre et al., 2007[4]
	Wegener's granulomatosis	cANCA antigens	Proteinase-3	?+	
	Microscopic polyangiitis	pANCA antigens	Myeloperoxidase	?+	Daiyasu and Toh, 2000
Non-Organ Specific	Systemic lupus erythematosus	Nucleosomes Ribonucleoproteins Phospholipid	DNA, U1RNP, Sm, Ro, La B2-glycoprotein-1		

[+] Signifies existence of bacterial orthologs.
[a] Bocquet N, Prado de Carvalho L, Cartaud J, Neyton J, Le Poupon C, Taly A, Grutter T, Changeux J-P, Corringer P-J. A prokaryotic proton-gated ion channel from the nicotinic acetylcholine receptor family. Nature 2007;445:116–9.
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[d] Forterre P, Gribaldo S, Gadelle D, Serre M-C. Origin and evolution of DNA topoisomerases. Biochimie 2007;89:427–46.

covery of autoantigens within the nucleus and other organelles, for which the autoantibody response is exquisitely antigen- and, in many cases, disease-specific. In parallel, there is accumulating evidence that some antigens are directly involved in pathogenesis.

Most autoimmune diseases have only a small number of associated autoantigens; some examples are shown in Table 1. While no doubt others will be discovered, the repertoire of human autoantibodies is relatively small (no more than a few hundred autoantigens) compared to around 21,000 genome-encoded proteins, implying considerable selectivity of the autoimmune response. Many autoantigens are members of evolutionarily conserved protein families which originated before the divergence of the prokaryotic and eukaryotic lineages. In this review we consider those autoantigens for which antibodies are diagnostically and/or