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Alpha-enolase: A target of antibodies in infectious and autoimmune diseases

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Received 2 September 2006; accepted 31 October 2006
Available online 1 December 2006

Abstract

Alpha-enolase, also called non-neuronal enolase, belongs to a family of cytoplasmic and glycolytic enzymes. In addition to its glycolytic function, alpha-enolase exerts many other functions in eukaryotes and prokaryotes. Antibodies (Abs) against alpha-enolase have been detected in a large variety of infectious and autoimmune diseases. These Abs might arise as a consequence of a microbial infection or uncontrolled growth or proliferation of cells in specific organs in pathophysiological conditions. In infections, anti-alpha-enolase Abs could play a role in limiting microbial tissue invasion. In autoimmune and inflammatory diseases, anti-alpha-enolase Abs could induce endothelial injury through the generation of immune complexes and activation of the complement classical pathway, inhibit the binding of plasminogen to alpha-enolase with perturbations of the intravascular and pericellular fibrinolytic system, and induce cell death through an apoptotic process. However, further studies are needed to improve our knowledge on the pathogenic role of these Abs.
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Keywords: Alpha enolase; Antibody; Inflammation; Infectious diseases; Autoimmune disease; Plasminogen

Contents

Abbreviations: Ab, antibody; ANCA, anti-neutrophil cytoplasm Abs; SLE, systemic lupus erythematosus; MC, mixed cryoglobulinemia; SSc, systemic sclerosis; RA, rheumatoid arthritis; HE, Hashimoto's encephalopathy; CAR, cancer-associated retinopathy.

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doi:10.1016/j.autrev.2006.10.004

1. Introduction

Mammalian enolases constitute a family of cytoplasmic and glycolytic enzymes. Enolases family is composed of 3 isozyme subunits, alpha, beta and gamma, which can form homodimers or heterodimers and are cell-type and development-specific: alpha-enolase (also called non-neuronal enolase) is ubiquitous and expressed in the early stage of embryonic development, beta-enolase is expressed in adult skeletal and cardiac muscles, and gamma-enolase (also called neuron-specific enolase) is expressed in mature neuron and neuroendocrine tissues. Alpha-enolase catalyzes the dehydration of 2-phosphoglycerate to phosphoenolpyruvate. In addition to its glycolytic function, alpha-enolase performs many functions in eukaryotes and prokaryotes, and plays an important role in various pathophysiological processes [1]. Antibodies (Abs) against alpha-enolase have been detected in a large variety of infectious and autoimmune diseases. However, the reasons why the spectrum of associated-diseases is so wide and the pathogenic role of these auto-Abs remain unclear. We here propose to review the current knowledge on anti-alpha-enolase Abs in infectious and autoimmune diseases, with a specific focus on the potential pathophysiological role of these auto-Abs.

2. Alpha-enolase: structure, subcellular location and function

Alpha-enolase enzyme is composed of two subunits of 433 amino-acids, with a molecular weight of approximately 47 kDa each, for which magnesium is required for stabilizing the dimer. Despite the differences found in species, alpha-enolase is highly conserved, with a 40 to 90% identity between enolases from two different species [1]. Group A streptococcus and *Saccharomyces cerevisiae* enolases share 43% and 62% homology with human alpha-enolase, respectively. Analysis of the crystal structure of *S. pneumoniae* alpha enolase reveals that it is in fact an octamer (a tetramer of dimers) with a molecular weight of 370 kDa [2]. Human beta and gamma-enolase share 83% homology each with human alpha-enolase [1].

Although alpha-enolase is an ubiquitous enzyme that is abundantly expressed in cytoplasm, it is most highly expressed in the kidney and thymus [3]. Its expression varies according to the conditions of cells. Alpha-enolase is expressed at the surface of many eukaryotic cells, such as stimulated hematopoietic cells (neutrophils, B and T lymphocytes, monocytes), epithelial, neuronal and endothelial cells [1,4–7]. In prokaryotic cells, alpha-enolase has been also detected at the surface of various *Streptococcus* species. The membrane translocation of the enzyme involves the hydrophobic domain of alpha-enolase and is allowed through post-translational modifications such as acylation or phosphorylation. Finally, alpha-enolase has been detected in the nucleus, exhibiting a role of Myc-binding protein (MBP-1) [1].

Alpha-enolase is a glycolytic enzyme that catalyzes the dehydratation of 2-phosphoglycerate to phosphoenolpyruvate [1]. Magnesium acts as a cofactor for enolase and sodium fluoride as an inhibitor. The bacteriostatic effect of fluoride in the dental plaque is thought to be the result of the inhibition of alpha-enolase in oral streptococcal species. In addition to its glycolytic function, alpha-enolase has many other functions related to its subcellular location [1]. In both eukaryotic and prokaryotic cells, cell-surface alpha-enolase serves as a strong receptor and activator of plasminogen, a key component of the intravascular and pericellular fibrinolytic systems [1,5]. In *S. pyogenes* infections, the binding of alpha-enolase to the cell-surface has been shown to play a crucial role in the pathogenesis [4], and is associated with the loss of its glycolytic activity and the acquisition of a high affinity for plasminogen [1,4]. The surface-exposed epitope involved in this function is located in the central loop of human alpha-enolase (amino-acids 257–272) [5]. The crystal structure study of alpha-enolase from *S. pneumoniae* reveals in fact the presence of two plasminogen binding sites. The first one matches the C-terminal lysyl residues but may not be as important as the second one since some alpha-enolases, including *C. albicans* alpha-enolase, entirely lack the first plasminogen binding site. In *S. pneumoniae*, the alpha-enolase binding to plasminogen induces plasminogen transformation into plasmin and is thought to be a virulence factor by preventing the generation of fibrin clots and thus enabling tissue invasion, as described for *S. pyogenes* and *S. pneumoniae* [4]. Alpha-enolase is also an eye tau-crystallin protein, exhibiting a structural role in lens and cataracts. When located in the nucleus, alpha-enolase is a Myc-binding protein (MBP-1), playing a crucial role in the regulation of cell growth and differentiation, as a negative regulator of the c-myc protooncogene leading to tumor suppression, and in the binding to cytoskeletal and chromatin structures. In addition, alpha-enolase is upregulated in endothelial cells in the context of hypoxic stress, providing protection to these cells by increasing anaerobic metabolism. Alpha-enolase is a Heat Shock Protein (HSP48) in *Saccharomyces cerevesiae* [1]. Finally, alpha-enolase may have a direct or indirect role in the site-specific organization of tubules [8].

3. Anti-alpha-enolase antibodies in infectious diseases

Antibodies against *S. pneumoniae* alpha-enolase develop early in life. Adrian et al., in a cohort study of children presenting with otitis media during their first two years of life, detected Abs against *S. pneumoniae*-alpha enolase in 99% of the sera [9]. The authors suggest the high prevalence of anti-alpha-enolase Abs in children to be due to cross-reactive epitopes of alpha-enolase from colonizing bacterial species because of the high degree of homology of alpha-enolase among these species [9]. Anti-alpha-enolase Abs, along with other anti-neuronal glycolytic enzymes, have been detected more frequently in patients with post-streptococcal neuropsychiatric sequelae as compared to controls [10]. Anti-alpha enolase Abs could play a role in limiting tissue invasion in *S. pyogenes* infections as shown by partial inhibition of plasminogen binding to pharyngeal cells in the presence of polyclonal anti-*S. pyogenes* alpha-enolase Abs [1]. Finally, anti-streptococcal enolase monoclonal Abs inhibit phagocytosis of the bacteria by human neutrophils [4]. Antibodies against *C. albicans* alpha-enolase are present in the sera of immunocompetent subjects in case of colonization with *C. albicans*. For immunodeficient patients, the rates of Abs against *C. albicans* alpha-enolase are significantly higher in the sera of patients with invasive candidiasis than in the sera of patients colonized with *C. albicans* and anti-alpha-enolase Abs can thus be used as a diagnostic test for systemic candidiasis [11].

4. Anti-alpha-enolase antibodies in systemic autoimmune disorders

Anti-alpha-enolase Abs have been found in a large variety of autoimmune and inflammatory diseases. Anti-alpha-enolase Abs have been initially reported in sera from patients that reacted with centrosomes in systemic rheumatic diseases [8]. Then, anti-alpha-enolase Abs have been shown to be a minor target antigen of anti-neutrophil cytoplasm Abs (ANCA) in systemic vasculitides [12], ulcerative colitis and Crohn's disease [13], and primary sclerosing cholangitis [14]. Since then, anti-alpha-enolase Abs have also been found in a large variety of autoimmune and inflammatory disorders such as systemic lupus erythematosus (SLE) [15], mixed cryoglobulnemia (MC) [15], systemic sclerosis (SSc) [15], rheumatoid arthritis (RA) [16], Behçet's disease [17], multiple sclerosis [18], Hashimoto's encephalopathy (HE) [19], paraneoplastic retinopathy such as cancer-associated retinopathy (CAR) [20] (Table 1). In healthy controls, Abs against alpha-enolase have been found in 0 to 6% [13,15,20–22]. The production of anti-alpha-enolase Abs is not isotype restricted [15].

Taking into account the wide spectrum of diseases associated with anti-alpha-enolase Abs, these Abs cannot help in the diagnosis of a specific autoimmune disease. However, anti-alpha-enolase Abs could be used as prognostic markers. In SLE and MC, the presence of anti-alpha-enolase Abs was associated with renal involvement [3,12,15], although this remains controversial [23]. In SSc, the number of patients tested was small and no correlation was clearly made between the detection of anti-alpha-enolase Abs and clinical manifestations, except for severe organ involvement [15]. In RA, the presence of anti-alpha-enolase Abs was associated with radiological progression [16]. In HE, high titers of anti-alpha-enolase Abs were associated with an excellent corticosteroid sensitivity [19,21]. In primary biliary cirrhosis, no correlation was found between the presence of anti-alpha-enolase Abs and clinical presentation, but the mortality rate associated with hepatic failure was significantly higher in patients with anti-alpha-enolase Abs [24].

The titer of anti-alpha-enolase Abs is high in systemic diseases, and relatively low in liver diseases, suggesting that the level of Ab affinity could play an important role, as well as differences in terms of Ab specificity. Indeed, the identification of reactivities with the different enolase isoforms (alpha, beta, gamma) in various autoimmune diseases suggest the recognition of different epitopes of enolase [15]. Moreover, reactivities between purified and recombinant alpha-enolase differ, suggesting the predominant recognition of post-translationally or post-traductionally modified forms of alpha-enolase, such as citrullination [25]. For example, the majority of sera tested in SLE, MC or HE expressed Ab reactivity toward alpha-enolase, whereas more than half of sera from patients with CAR [20] and lymphocytic hypophysitis [26] reacted either with alpha- or gamma-enolase.

Epitope-mapping was performed in CAR and in endometriosis. Four major epitopes of alpha-enolase (amino-acids 31–38, 176–183, 421–428 and 56–63) were found to be recognized by all anti-alpha-enolase Abs of CAR patients, the epitope 56–63 being specifically associated with pathogenic sera [27]. Interestingly, sera from healthy subjects recognized the epitopes 30–37, 176–183 and 421–428 of alpha-enolase but not the epitope 56–63 [27]. In endometriosis, anti-alpha-enolase Abs bound preferentially to two epitopes (53–87 and 207–238) [28], and shared the reactivity against the epitope 56–63 with CAR patients.

5. Pathogenic role of anti-alpha-enolase antibodies

Anti-alpha-enolase Abs might be produced after a contact with bacteria or yeast and cross react with human-

Table 1
Autoimmune and inflammatory disorders associated with anti-alpha-enolase Abs

Autoimmune diseases	Frequency of anti-enolase Abs	Detection method	References
Systemic lupus erythematosus	14/68 (21%)	IB	[23]
	5/26 (19%)	IB	[16]
	9/33 (27%)	IB	[15]
	10/41 (24%)	IB	[12]
SLE with active renal disease	6/9 (67%)	IB	[15]
	8/10 (80%)	IB	[12]
SLE with MN	4/9 (44%)	ELISA	[22]
Discoid lupus erythematosus	1/1	IB	[35]
Mixed cryoglobulinemia			
With renal involvement	6/19 (32%)	IB	[15]
	7/11 (64%)	IB	[3]
Without renal involvement	0/15 (0%)	IB	[15]
Mixed connective tissue disease			
Systemic sclerosis	2/13 (15%)	IB	[16]
	6/20 (30%)	IB	[15]
ANCA-positive vasculitides	22/59 (37%)	IB	[12]
Behçet's disease	18/40 (45%)	IB*	[17]
	15/40 (38%)	ELISA*	[17]
Rheumatoid arthritis			
RA	24/52 (46%)**	IB	[25]
	36/145 (25%)	IB	[16]
	2/35 (6%)	IB	[15]
RA with MN	10/15 (66%)	ELISA	[22]
Primary MN	60/87 (69%)	ELISA	[22]
Liver diseases			
Autoimmune hepatitis	10/18 (56%)	IB	[36]
	12/20 (60%)	ELISA	[14]
	6/19 (32%)	IB	[24]
Primary biliary cirrhosis	16/56 (29%)	IB	[24]
	6/20 (30%)	ELISA	[14]
Primary sclerosing cholangitis	5/15 (33%)	IB	[14]
	4/15 (27%)	ELISA	[14]
Inflammatory bowel disease			
Ulcerative colitis	10/96 (10%)	IB	[13]
Crohn's disease	20/112 (18%)	IB	[13]
Coeliac disease	6/13 (46%)***	IB	[37]
Multiple sclerosis	–	IB	[18]
Hashimoto's thyroiditis			
With encephalopathy	5/6 (83%)	IB	[19]
	3/5 (60%)	IB	[21]
Without encephalopathy	2/17 (12%)	IB	[19]
	3/54 (6%)	IB	[21]
Pituitary diseases			
Lymphocytic hypophysitis	7/17 (41%)	RLA	[38]
Pituitary adenoma	6/13 (46%)	RLA	[38]
ACTH deficiency	2/10 (20%)	RLA	[38]
Sheehan syndrome	2/3 (67%)	RLA	[38]
Retinopathy			
Autoimmune retinopathy	17/58 (29%)	IB	[39]
Paraneoplastic retinopathy (CAR)	11/33 (33%)	IB	[39]
Paraneoplastic retinopathy (CAR)	11/16 (69%)	IB	[20]
Cystoid macular edema	6/10 (60%)	IB	
Autoimmune polyglandular syndrome I	33/41 (80%)	IP	[40]
Endometriosis	21/41 (50%)	IB	[28]

Abs: antibodies; SLE: systemic lupus erythematosus; MN: membranous nephropathy; RA: rheumatoid arthritis; IB: immunoblot; ELISA: enzyme-linked immunosorbent assay; RLA: radioligand assay; IP: immunoprecipitation.
* IgMisotype. **Citrullinated α-enolase. ***IgA Isotype.

alpha-enolase [15]. Indeed, Fontan et al. suggested that Abs raised against streptococcal alpha-enolase during *S. pyogenes* infections might recognize common epitopes of human alpha-enolase expressed at the membrane of eukaryotic cells and could be involved in post streptococcal sequelae [4]. Interestingly, higher titers of anti-streptococcal alpha-enolase Abs are found in serum samples from patients with acute rheumatic fever as compared with healthy controls or patients with minor pharyngitis. The potential role of an immune response directed against yeast was supported by the binding of anti-alpha-enolase Abs from patients with autoimmune hepatitis and primary sclerosing cholangitis to *Saccharomyces cerevisiae* enolase. Also, in patients with a *Candida albicans* infection, yeast enolase is released [29] and may generate an immune response. Finally, particular immune background may play a role since it was shown that human alpha-enolase-derived peptides bound to HLA-DR8, suggesting the occurrence of autoimmune diseases in patients with HLA-DR8 allele [30].

The role of anti-alpha-enolase Abs has been extensively studied in patients with SLE related-nephritis and CAR. In patients with SLE related-nephritis, alpha-enolase was found to be overexpressed in glomeruli and inflammatory lesions such as crescents, whereas in normal kidney, alpha-enolase was almost undetectable in glomeruli and expressed only in tubuli [31]. Since the upregulation of alpha-enolase can increase the tolerance to hypoxia [1], anti-alpha-enolase Abs might be involved in the pathogenesis of SLE related-nephritis and act as a nephrogenic autoantigen. BALB/c mice were injected intraperitoneally with hybridoma-producing anti-alpha-enolase Abs, and some of the glomeruli showed focal infiltrates or diffuse proliferative lesions. Thus, since alpha-enolase is expressed on the membrane of various cells, anti-alpha-enolase Abs could play a role in renal and endothelial injury through the generation of immune complexes and activation of the complement classical pathway [15].

Anti-alpha-enolase Abs can inhibit the binding of plasminogen to alpha-enolase [32], and thus plasminogen activation to plasmin. As reported in SLE, in MC and SSc, anti-alpha-enolase Abs react with endothelial cells expressing large amounts of alpha-enolase, and induce injury to those cells. Moreover, anti-alpha-enolase Abs isolated from the serum of patients with SLE, MC or SSc bound to the membrane-associated form of the enzyme, interfering the plasminogen receptor function [32]. In addition, although hematopoietic cells display several molecules that bind plasminogen, alpha-enolase is responsible for the majority of the promotion of plasminogen activation on their surface, and a monoclonal anti-alpha-enolase Ab inhibit the cell-surface mediated plasminogen activation [33].

In CAR patients, anti-alpha-enolase Abs are capable of penetrating retinal tissue to target ganglion cell layer and inner nuclear layers and, consequently, induce death of E1A.NR3 retinal cells through an apoptotic process [34]. Cytotoxicity of CAR Abs occur independently of complement activation and is dependent on the amount of Abs added and the duration of exposure of retinal cells to these Abs. Moreover, when anti-alpha-enolase Abs were injected intravitreously into rat eyes, these Abs also targeted retinal cells in the inner nuclear layer and ganglion cell layer, and consequently caused apoptotic cell death [34]. Interestingly, it was reported that anti-alpha-enolase Abs from patients with CAR, patients with endometriosis or healthy individuals did not bind to the epitope 257–272, involved in the plasminogen-binding of alpha-enolase, suggesting that these conditions are not associated with perturbations of the intravascular and pericellular fibrinolytic system.

In conclusion, anti-alpha-enolase Abs have been found in a large variety of autoimmune and inflammatory diseases. These Abs might arise as a consequence of a streptococcal infection or uncontrolled growth or proliferation of cells in specific organs in autoimmune and/or inflammatory diseases [27]. Further studies are needed to improve our knowledge on the pathogenic role of Abs against alpha-enolase.

Acknowledgements

This work is supported by grants from the Association des Sclérodermiques de France (ASF) and the Legs POIX, Chancellerie des Universités, Académie de Paris, France. Benjamin Terrier received a financial support from the Direction régionale des Affaires Sanitaires et Sociales. Philippe Guilpain is on a grant from the “Fondation pour la Recherche Médicale (FRM)”; Amélie Servettaz is on a grant from Actelion and the “Association des Sclérodermiques de France”. Amélie Servettaz and Luc Mouthon are members of the Groupe Français de Recherche sur la Sclérodermie.

Take-home messages

- Alpha-enolase (also called non-neuronal enolase) is a ubiquitous glycolytic enzyme that exert many other functions in eukaryotes and prokaryotes, including the ability to bind to plasminogen and induce its transformation into plasmin.

- Antibodies (Abs) against alpha-enolase have been detected in a large variety of infectious and autoimmune diseases.
- In infectious diseases, anti-alpha enolase Abs could play a role in limiting the microbial tissue invasion.
- In autoimmune and inflammatory diseases, anti-alpha-enolase could induce endothelial injury through the generation of immune complexes and activation of the complement cascade, inhibit the binding of plasminogen to alpha-enolase with perturbations of the intravascular and pericellular fibrinolytic system, and induce cell death through an apoptotic process.

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Platelet autoantibodies are common in hepatitis C infection, irrespective of the presence of thrombocytopenia

To investigate the generation of platelet antibodies in hepatitis C virus (HCV)-infected individuals and their relation to the development of thrombocytopenia. In this study, Panzer S. et. al. (Eur J Haematol 2006; 77:513-7) tested by the monoclonal antibody-spTo investigate the generation of platelet antibodies in hepatitis C virus (HCV)-ecific immobilization of platelet antigen assay (MAIPA) for the presence of platelet antibodies against specific glycoprotein (GP) targets (GPIIb/IIIa, GPIb/IX, GPIa/IIa, GPIIIb, GPV, and FcRgammaIIa) in 48 HCV-infected individuals of various stages of disease and compared the results with those from 35 patients with alcoholic liver cirrhosis. Thirty-two HCV-infected individuals (66%) had detectable platelet antibodies. The most common target was GPIIb/IIIa, but all other GP were also targets. Results were not different from patients with alcoholic liver cirrhosis. There was no correlation between antibodies and platelet counts, or the stage of disease, or the viral genotype, or a discernible influence of treatment with alpha-interferon. While platelet autoantibodies are common in individuals with HCV infection, their detection does not assist in the diagnosis of immune thrombocytopenia.

Correlation of initial autoantibody profile and clinical outcome in primary biliary cirrhosis

Although there have been significant advances in understanding the clinical and biochemical features of primary biliary cirrhosis (PBC), there is still a paucity of data on the usefulness of biomarkers as prognostic indicators. This is particularly important at the time of initial diagnosis. Indeed, the widespread use of antimitochondrial antibody testing has led to an earlier diagnosis of asymptomatic PBC and it is difficult to predict which patients will experience a benign versus a rapidly progressive course. To address this issue, Wesierska-Gadek J. et. al. (Hepatology 2006; 43: 1135-44) examined a uniaue population of 127 newly diagnosed patients with PBC during a 15-year period of observation that began in January 1990. Sera from these patients were analyzed for antimitochondrial, antinuclear, and anti-smooth muscle antibodies, and immunoblotting was performed for nuclear pore complex (NPC). Among patients with early disease, bilirubin increased to > 2 mg/dl in the anti-NPC (+) patients (26% vs 5%, $p = 0.019$). Anti-NPC antibodies remained stable or slightly increased over the period of observation. In conclusion, anti-NPC identifies patients likely to experience an unfavorable clinical course and more rapid disease progression.