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THEMATIC SERIES ''ALPHA-1 ANTITRYPSIN DEFICIENCY'' - ARTICLE IN ENGLISH AND FRENCH
Coordinated by J.-F. Mornex and A. Cuvelier

Molecular pathogenesis of alpha-1-antitrypsin deficiency

Bases moléculaires du déficit en alpha-1 antitrypsine

A. Duvoix, B.D. Roussel, D.A. Lomas*

Department of Medicine, University of Cambridge, Cambridge Institute for Medical Research, Wellcome Trust/MRC Building, Hills Road, Cambridge, CB2 0XY, UK

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Summary Alpha-1 antitrypsin (α_1-AT) is the most abundant circulating protease inhibitor. The common severe Z allele of α_1-AT (Glu342Lys) causes the protein to form ordered polymers that are retained within the endoplasmic reticulum of hepatocytes. These polymers form the periodic acid-Schiff positive inclusions that are associated with cirrhosis. The lack of circulating α_1-AT predisposes the Z α_1-AT homozygote to early onset emphysema. We review here the molecular basis of α_1-AT deficiency and show how understanding the liver disease provides new insights in the pathobiology of the associated emphysema. The mechanism of α_1-AT deficiency provides a paradigm for a wider group of conditions that we have termed the serpinopathies. We also examine the strategies that are being pursued to develop novel therapies for α_1-AT deficiency. This review considers our understanding of the pathobiology of α_1-AT deficiency and then illustrate the therapeutic possibilities that can ensue once we understand basic mechanisms of disease.

MOTS CLÉS
Déficit en alpha-1 antitrypsine ;
Maladie hépatique ;

Résumé L'alpha-1 antitrypsine (α_1-AT) est le principal inhibiteur circulant des protéases. La mutation délétère de l'allèle Z de l'α_1-AT (Glu342Lys) entraîne la formation de polymères ordonnés de la protéine qui sont séquestrés à l'intérieur du réticulum endoplasmique des hépatocytes. Ces polymères forment des inclusions PAS (acide périodique de Schiff) positives qui

* Corresponding author.
E-mail address: dal16@cam.ac.uk (D.A. Lomas).

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sont associées à une cirrhose. Le déficit en α_1-AT circulante prédispose les individus homozygotes pour l'allèle Z de l'α_1-AT au développement précoce d'un emphysème pulmonaire. Dans ce manuscrit, nous passons en revue les bases moléculaires du déficit en α_1-AT et montrons comment la compréhension de la maladie hépatique apporte de nouvelles perspectives aux modifications physio-pathologiques qui conduisent à l'emphysème associé. Le mécanisme sous-jacent au déficit en α_1-AT permet de proposer un paradigme à un groupe plus important de pathologies que nous avons appelées les serpinopathies. Nous abordons également les stratégies de développement des nouvelles thérapies pour traiter le déficit en α_1-AT. Cette revue porte sur notre compréhension de la biopathologie du déficit en α_1-AT et illustre les possibilités thérapeutiques pouvant découler de notre compréhension des mécanismes fondamentaux de la maladie.

English version

Alpha-1 antitrypsin (α_1-AT) is synthesized by the liver and is present in the plasma at a concentration of 1.5—3.5 g/L. It functions primarily as an inhibitor of the enzyme neutrophil elastase. Most individuals are homozygous for the M allele with the commonest deficiency alleles being the severe Z (Glu342Lys) and the mild S (Glu264Val) variants. The Z mutation causes α_1-AT to be degraded by endoplasmic reticulum-associated degradation (ERAD) or retained within hepatocytes as polymers that form periodic acid-Schiff (PAS) positive, diastase resistant inclusions [1] (Fig. 1A). These inclusions are associated with neonatal hepatitis, cirrhosis and hepatocellular carcinoma [2,3]. Only 10—15% of Z α_1-AT is folded and released into the circulation. This leaves the lungs exposed to enzymatic damage by neutrophil elastase and so predisposes the Z homozygote to early onset panlobular emphysema (see later). The S allele results in less retention of protein within hepatocytes with plasma levels being 60% of those of the M allele. This does not result in any clinical sequelae.

Protein conformational changes

Biochemical, biophysical and crystallographic studies have been used to dissect the molecular basis by which monomeric Z α_1-AT forms polymers. The Glu342Lys mutation associated with the Z allele is located at the head of strand 5 of β-sheet A and the base of the mobile reactive loop (Fig. 1B). This mutation causes a conformational transition and the formation of an unstable intermediate termed M* in which β-sheet A opens and the upper part of helix F unwinds [4—6]. The patent β-sheet A can then accept the loop of another molecule to form a loop-sheet dimer, which extends to form longer chains of loop-sheet polymers (Fig. 1B). There is evidence that it is the dimer that initiates and propagates polymerisation of α_1-AT [7].

A more recent suggestion is that polymers are formed by a larger domain swap involving exchange of the reactive centre loop and strand 5A. This is based on the crystal structure of a dimer of antithrombin [8]. The authors argue that polymers form whilst the protein is folding rather than from protein with a near-native structure. Indeed there is strong evidence that mutants of both α_1-AT and neuroserpin

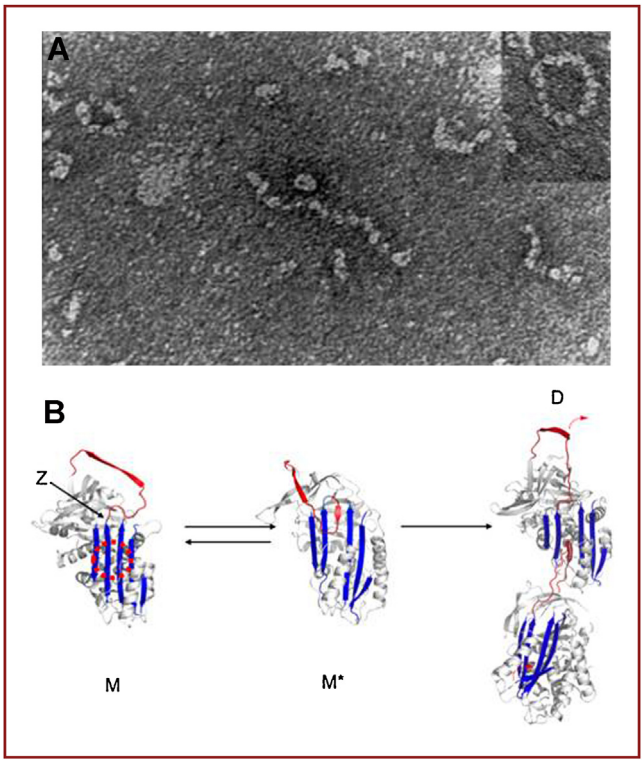

Figure 1. The molecular basis of α_1-AT deficiency. A. The intrahepatic polymers of mutant Z α_1-AT have a ''beads on a string appearance'' on electron microscopy. Reproduced from [13]. B. The pathway of serpin polymerisation. The structure of α_1-AT (M) is centred on β-sheet A (blue) and the mobile reactive centre loop (red). The Z mutation at the base of the reactive loop (arrowed) and mutations in the shutter domain (red circle) result in the formation of an unstable intermediate (M*) that has an open β-sheet A. This patent β-sheet A can either accept the loop of another molecule to form a dimer (D) which then extends into polymers. The red arrow shows the linkage of the reactive centre loop.

are associated with a significant delay in folding [9,10]. This folding defect can be studied by treating the folded protein with urea or guanidine. However, in the case of α_1-AT the polymers that form as a consequence of treatment with these agents or at low pH are not recognised by a monoclonal antibody that recognises the pathological polymers that form in vivo [11]. This implies that the long-lived