Reducing the amyloid burden through immunotherapy: a major therapeutic advance*

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Pepys and coworkers report in a recent paper (Bodin et al., Nature 2010; 468:93–97 [1]), the rapid resorption of visceral amyloid using antibodies to a common constituent of all amyloid deposits, the serum amyloid P component (SAP), in a human SAP transgenic mice model of reactive amyloidosis (AA amyloidosis) [1]. SAP binds avidly to all types of amyloid fibrils and protects them from proteolytic degradation and resorption. In order to promote the resorption of amyloid deposits, Pepys and coworkers had previously designed the palindromic molecule (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) that bound with high affinity human SAP and triggered its rapid clearance by the liver, thus depleting circulating SAP [2]. However, some SAP is left bound to amyloid even after months of CPHPC treatment [3]. Now they report that targeting this residual SAP with anti-SAP antibodies after treatment with CPHPC triggered the complement-dependent phagocytic clearance mechanisms that rapidly removed visceral AA amyloid deposits in mice. The authors cautioned that systemic amyloidosis patients have widespread amyloid deposits in sensitive tissues, including the heart, blood vessel walls and nerves, which are not involved in the mouse AA model. Also, the trace amount of human SAP in normal glomerular basement membrane and elastic fiber microfibrils is a potential undesirable target for anti-SAP antibodies. However, no adverse events were noted and no change in plasma biochemistry or any histological abnormality was observed. This important paper highlights the feasibility and efficacy of immunotherapy in amyloid diseases.

Translational medicine in systemic amyloidoses

The amyloidoses constitute a large group of diseases [4] characterized by deposition of misfolded proteins as fibrillar aggregates in target organs whose functions progressively deteriorate [5,6]. Renal dysfunction, which frequently progresses to end-stage renal disease (ESRD), is the commonest clinical manifestation of systemic amyloidoses, and diagnosis is frequently obtained through renal histology [7]. Systemic amyloidoses are of great relevance for the nephrologist, who is involved both in the diagnosis and in the care of these diseases, playing an essential role in supporting the life of patients who have reached ESRD with dialysis.

Systemic amyloidoses represent a perfect field for translational medicine. During the last decade, fundamental advancements have been made in understanding the molecular mechanisms of the disease, and novel therapeutic approaches have been developed thanks to a deeper knowledge of the molecular processes involved in the pathogenic cascade. This translational process is exemplified in Figure 1 that summarizes the events involved in the formation of AA amyloidosis [8], the same type of amyloidosis reproduced in the mice model used in the paper under discussion. The knowledge of the key events in the amyloidogenic cascade has stimulated the development of targeted therapies that complement the treatments for the control of the underlying diseases. The anti-cytokine biological agents have resulted in significant reduction in the concentration of the serum amyloid A (SAA) protein, with frequent resolution of amyloid-related kidney dysfunction, such as regression of nephrotic syndrome [9]. A compound interfering with the binding of glycosaminoglycans to the amyloid proteins (eprodisate, a small sulfonated molecule with structural similarity to heparan sulfate) was found to have a beneficial effect on the rate of deterioration of renal function [10]. SAP can be cleared from amyloid deposits using small palindromic drugs (CPHPC) [2] and, as reported by Pepys and coworkers, the clearance of amyloid deposits can be promoted and accelerated by combining CPHPC with anti-SAP immunotherapy [1]. Active and passive immunotherapy is under intense investigation for the treatment of Alzheimer’s disease [11] and an anti-light chain antibody is being developed for the imaging and treatment of light chain amyloidosis (AL) [12]. The Pepys’ approach has the advantage of being potentially applicable to
all forms of systemic amyloidosis since it is directed against the common constituent SAP.

Ultimately, amyloid diseases will be treated with a combination of approaches that reduce protein precursor production, prevent aggregation and induce resorption of amyloid deposits.

**Recovery of damaged vital organs**

Several lines of evidence indicate that amyloidogenic precursors and amyloid fibrils both contribute, in different ways and to a different extent, to the manifestations of systemic amyloidosis-associated organ dysfunction. On one hand, clinical observations indicate that amyloid deposits are usually associated with organ dysfunction. However, the elimination of the soluble fibrillar precursor may be associated with the recovery of organ function, despite the persistence of unmodified amyloid deposits. In addition to sporadic cases [13,14], renal recovery has been reported in several patients with AA amyloidosis in association with a stable amyloid burden and a low concentration of serum SAA [15]. Furthermore, we and others have reported that in patients with light chain amyloidosis, a significant reduction or elimination of circulating amyloidogenic light chains through chemotherapy translates into rapid recovery of heart function, with a prompt reduction of biomarkers of cardiac dysfunction (natriuretic peptide type B) and damage (troponins), despite the unwavering persistence of amyloid deposits in the myocardium as assessed by echocardiography [16–18]. Tissue damage may require the presence of both components: amyloid fibrils and soluble amyloidogenic protein species [19]. The combination of agents aiming to reduce the concentration of the amyloidogenic protein, with those favoring the clearance of amyloid deposits may accelerate the recovery of damaged vital organs.

**Clinical implications**

ESRD is associated with increased morbidity and mortality in patients with amyloidosis [15]. For the practicing nephrologist, it is essential to rescue the function of the compromised kidney. Early and accurate diagnosis remains the key to reaching this goal, and all means should be used to increase the awareness and knowledge of these complex diseases. At present, the mainstay of treatment is aimed at reducing the production of the amyloidogenic protein. In AL amyloidosis, the introduction of novel potent drugs targeting the amyloidogenic plasma cell clone has produced significant and marked improvement in the survival in the past decade [20]. In the near future, this approach will be combined with several drugs targeting key elements in the amyloid cascade and preventing further deposition and progression of organ damage. Removing existing amyloid deposits through immunotherapy, as reported by Pepys and coworkers represents a major therapeutic advance that will hopefully be an asset in the clinical setting.

These effective novel therapeutic opportunities should raise the awareness of the clinician of these complex diseases in order to diagnose them in the earlier stages, when full recovery of vital organ function can still be achieved through a concerted therapeutic approach.

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**References**


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