Amyloid β2-Microglobulin

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Abstract

Dialysis-related amyloidosis (DRA), which is an inevitable complication of long-term haemodialysis (HD), manifests major clinic-pathological characteristics, including carpal tunnel syndrome, which is the most common clinical sign; systemic involvement of many articular tissues; and the presence of β2-microglobulin (β2M) as a precursor protein in this amyloidosis.

Keywords: Dialysis-related amyloidosis; β2-microglobulin; Haemodialysis

Introduction

Amyloid is a fibrillar protein and is primarily a conformational variant of an originally globular precursor protein. β2M is an essential protein for normal conformation of major histocompatibility complex class I molecules on cell membranes and is degraded mainly in renal proximal tubules. β2M passes freely across vascular walls. Therefore, serum levels of β2M are extremely high in patients undergoing HD. Although HD can clear as much as 70% of circulating β2M, β2M in the interstitial space can accumulate and progressively lead to development of DRA [1]. The amyloid processes may occur in the interstitial space. We have studied the amyloidogenicity of β2M and found a previously unknown amyloidogenic process, which we describe in this short review.

Specific information about the different β2M structures follows here:

The three-dimensional structure (conformation) of β2M: β2M consists of 99 amino acids. The three-dimensional structure of native β2M is formed by the folding of seven peptide segments (strands) into a globular conformation, with both the N-terminal and the C-terminal segments folded inward from the molecular surface. McParland et al. demonstrated that unfolding in β2M started first in the N-terminal segment and then continued in the C-terminal segment [2].

The intermediate structure of β2M: Several basic studies described a conversion process in which amyloid protein is formed. In this process, the folded conformation, i.e., native β2M is unfolded into a partially unfolded conformer, i.e., the intermediate species. The amyloid protein is insoluble, but the intermediate species is soluble and can be identified directly, with native β2M, via capillary electrophoresis. By using this technique [3], we confirmed that β2M in serum consisted of two forms, the folded native β2M (N-β2M) and the partially unfolded intermediate β2M (I-β2M) in both healthy persons and patients undergoing HD (Figure 1) [4,5].

Figure 1: Native β2M (N-β2M) and intermediate β2M (I-β2M) as determined with capillary electrophoresis. Unpublished data for n=30 HD patients.

C-terminal unfolding and β2M 92-99: Stoppini et al. first implicated the C-terminal region of β2M in amyloidogenicity by using a monoclonal antibody specific for the C-terminal eight amino acids [6]. We then reported on β2M with an unfolded C-terminal region, i.e., β2M 92-99, in amyloid tissues from patients undergoing HD [7]. However, we did not detect β2M 92-99 in serum from patients undergoing HD because the C-terminal
region in I-β2M may be not completely unfolded as is the case for β2M 92-99 [8].

ΔN6β2M: In 1987, Linke et al. first reported a variant of β2M lacking the six N-terminal amino acids, i.e., ΔN6β2M, in patients undergoing HD [9]. Esposito et al. and others then confirmed that ΔN6β2M was a highly amyloidogenic variant [10,11]. We recently reported that the C-terminal region was completely unfolded in ΔN6β2M as well as in β2M 92-99 [8].

Glycosaminoglycans (GAGs) and heparin: GAGs including heparin are an essential component of interstitial tissue. In addition, heparin is most often used as an anti-coagulant in the clinical setting of HD. Several studies showed that GAGs facilitate the amyloidogenicity of β2M [12,13], and we also found that heparin promoted β2M unfolding [14].

The working hypothesis: N-β2M coexists with I-β2M at a ratio of 10:1 in body fluids, and the HD procedure causes a shift from N-β2M toward I-β2M. GAGs in the interstitial space promote unfolding of the C-terminal region of I-β2M to generate β2M 92-99. β2M 92-99 cannot be refolded or returned to the vascular space. An accumulation of ΔN6β2M 92-99 leads to the generation of amyloid β2M in the interstitial space (Figure 2).

ΔN6 β2M aptamer: We recently showed that an aptamer for ΔN6 β2M has a domain for the C-terminal region and could block amyloid fibril formation in-vitro [15].

Conclusion

Amyloidosis, including DRA and Alzheimer disease, is becoming a major clinical entity. Amyloidosis is a disease of misfolded precursor proteins. Thus far, we have demonstrated that misfolding of β2M is initiated by an unfolding of the C-terminal segment of β2M, and GAGs in interstitial tissue are intimately associated with the completion of the C-terminal unfolding of β2M. We believe that an intermediate β2M with an unfolded C-terminal may be a key intermediate molecule for amyloid β2M, as (Figure 2) illustrates. The data related to the ΔN6 β2M aptamer support our belief.

References