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Amyloid β_2-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 β_2-microglobulin (β_2M) as a precursor protein in this amyloidosis.

Keywords: Dialysis-related amyloidosis; β_2-microglobulin; Haemodialysis

Introduction

Amyloid is a fibrillar protein and is primarily a conformational variant of an originally globular precursor protein. β_2M 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. β_2M passes freely across vascular walls. Therefore, serum levels of β_2M are extremely high in patients undergoing HD. Although HD can clear as much as 70% of circulating β_2M, β_2M 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 β_2M and found a previously unknown amyloidogenic process, which we describe in this short review.

Specific information about the different β_2M structures follows here:

The three-dimensional structure (conformation) of β_2M: β_2M consists of 99 amino acids. The three-dimensional structure of native β_2M 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 β_2M started first in the N-terminal segment and then continued in the C-terminal segment [2].

The intermediate structure of β_2M: Several basic studies described a conversion process in which amyloid protein is formed. In this process, the folded conformation, i.e., native β_2M 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 β_2M, *via* capillary electrophoresis. By using this technique [3], we confirmed that β_2M in serum consisted of two forms, the folded native β_2M (N-β_2M) and the partially unfolded intermediate β_2M (I-β_2M) in both healthy persons and patients undergoing HD (**Figure 1**) [4,5].

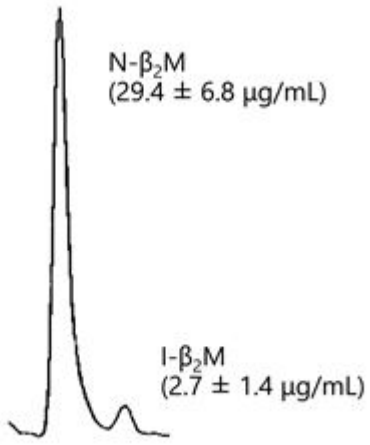

Figure 1: Native β_2M (N- β_2M) and intermediate β_2M (I- β_2M) as determined with capillary electrophoresis. Unpublished data for n=30 HD patients.

C-terminal unfolding and β_2M 92-99: Stoppini et al. first implicated the C-terminal region of β_2M in amyloidogenicity by using a monoclonal antibody specific for the C-terminal eight amino acids [6].We then reported on β_2M with an unfolded C-terminal region, i.e., β_2M 92-99, in amyloid tissues from patients undergoing HD [7]. However, we did not detect β_2M 92-99 in serum from patients undergoing HD because the C-terminal

region in I-β_2M may be not completely unfolded as is the case for β_2M 92-99 [8].

ΔN6β_2M: In 1987, Linke et al. first reported a variant of β_2M lacking the six N-terminal amino acids, i.e., ΔN6β_2M, in patients undergoing HD [9]. Esposito et al. and others then confirmed that ΔN6β_2M was a highly amyloidogenic variant [10,11]. We recently reported that the C-terminal region was completely unfolded in ΔN6β_2M as well as in β_2M 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 β_2M [12,13], and we also found that heparin promoted β_2M unfolding [14].

The working hypothesis: N-β_2M coexists with I-β_2M at a ratio of 10:1 in body fluids, and the HD procedure causes a shift from N-β_2M toward I-β_2M. GAGs in the interstitial space promote unfolding of the C-terminal region of I-β_2M to generate β_2M 92-99. β_2M 92-99 cannot be refolded or returned to the vascular space. An accumulation of β_2M 92-99 leads to the generation of amyloid β_2M in the interstitial space (**Figure 2**).

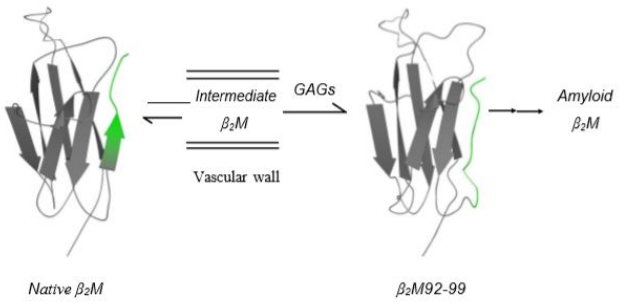

Figure 2: Unfolding processes that leads to formation of amyloid β_2M.

ΔN6 β_2M aptamer: We recently showed that an aptamer for ΔN6 β_2M 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 β_2M is initiated by an unfolding of the C-terminal segment of β_2M, and GAGs in interstitial tissue are intimately associated with the completion of the C-terminal unfolding of β_2M. We believe that an intermediate β_2M with an unfolded C-terminal may be a key intermediate molecule for amyloid β_2M, as (**Figure 2**) illustrates. The data related to the ΔN6 β_2M aptamer support our belief.

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