MICROGLOBULIN-DERIVED AMYLOID IN DIALYSIS PATIENTS

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In the recent past, a whole spectrum of osteoarticular problems has been recognized in patients on longterm hemodialysis. After the recognition by Assenat et al. (1) of amyloid-related carpal tunnel syndrome in hemodialysis patients whose primary renal disease had not been amyloidosis, many reports confirmed its high prevalence in dialysis patients (2). In addition, joint pain, joint swelling and recurrent hemarthros were recognized as the consequence of synovial amyloid deposits (3) which had many similarities with articular amyloidosis of the AL type (4). Finally, amyloid containing bone cysts, pathological fractures (5) and destructive arthropathy in the appendicular or axial skeleton (6) were noted with increasing frequency. Todate, this new form of amyloid has not been demonstrated in non-dialysed uremic patients. However, in patients with preterminal renal failure, similar amyloid has been recognized as a structural component of matrix stones either within the kidney or passed into the urine (7,8).

While extrarenal amyloid, todate, has only been demonstrated in patients on renal replacement therapy, i.e. hemodialysis, hemofiltration or CAPD (9), it is unknown whether the phenomenon is causally related to these treatment modalities or whether it merely reflects longer patients survival and continued exposure to risk. It came as a major breakthrough when such amyloid could be characterized at the molecular level by Gejyo(10). He documented that these amyloid fibrils are derived from the circulating precursor molecule beta-2-microglobulin ($\beta_2m$). The clinical problems of dialysis-related amyloid have been reviewed extensively elsewhere (9,11). This communication will mainly discuss problems of pathogenesis and treatment.

1. The $\beta_2m$ molecule

As shown in fig. 1, $\beta_2$ microglobulin is the light chain of class I major histocompatibility protein antigen (MHC-I). It is composed of 100 amino acids and has a relative molecu-
lar mass of 11,700 Dalton. With respect to amino acid sequence and conformation, striking homologies exist with the immunoglobulin L-chain, the precursor of another form of amyloid (AL-amyloid).

Analysis of the three dimensional structure of $\beta_2m$ indicates that more than 50% of the molecular is in beta pleated sheet conformation, i.e. the conformation exhibited by amyloid fibrils (12). $\beta_2m$ is localized exterior to the plasma membrane without being covalently attached to the HLA class I molecule. Consequently, membrane $\beta_2m$ can exchange with circulating $\beta_2m$ (13). Cell lines of different origin synthesize and secrete free $\beta_2m$, suggesting imbalance of synthesis of the two HLA antigen subunits (14), similar to the known disproportionate synthesis of light and heavy immunoglobulin chains. Expression of MHC class I antigens, and in parallel of $\beta_2m$, can be induced by numerous signals, e.g. alpha- and gamma-interferon, mitogens, antigens, growth factors or endotoxin (15,16). Stimulation by antigens and cellular growth factors may explain why plasma $\beta_2m$ concentrations are elevated in patients with chronic bacterial infections, rheumatological diseases or immuno-regulatory disturbances, e.g. SLE or AIDS, and in malignancies. The main source of circulating $\beta_2m$ has commonly been thought to be the cells of the immune system, but recent evidence showed that $\beta_2m$ is a true secretory protein of hepatocytes, the synthesis of which is modulated by IFN but not by IL-1 (17), as demonstrated on the protein and RNA level. As expected from its molecular weight, $\beta_2m$ is distributed in the extracellular space (18) and cleared by glomerular filtration (19,20). Consequently, in patients with reduced renal function, terminal elimination half life is prolonged (18) and in endstage renal failure plasma levels may be elevated up to 60-fold (19). When human $\beta_2m$ is injected into nephrectomized rats, extrarenal elimination or biodegradation accounts for less than 3% of total metabolic clearance (20). It is interesting that after injection of labelled $\beta_2m$, tracer uptake by organs in nephrectomized animals parallels their macrophage content - a possible hint as to the site of biodegradation, if this occurs, in the

![Fig. 1 Schema of molecular structure of IgG and HLA antigen class I.](image-url)