Matrix Metalloproteinases and Their Tissue Inhibitors in Cardiac Amyloidosis

Relationship to Structural, Functional Myocardial Changes and to Light Chain Amyloid Deposition

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Background—Cardiac amyloidosis is characterized by amyloid infiltration resulting in extracellular matrix disruption. Amyloid cardiomyopathy due to immunoglobulin light chain protein (AL-CMP) deposition has an accelerated clinical course and a worse prognosis compared with non–light chain cardiac amyloidoses (ie, forms associated with wild-type or mutated transthyretin [TTR]). We therefore tested the hypothesis that determinants of proteolytic activity of the extracellular matrix, the matrix metalloproteinases (MMPs), and their tissue inhibitors (TIMPs) would have distinct patterns and contribute to the pathogenesis of AL-CMP versus TTR-related amyloidosis.

Methods and Results—We studied 40 patients with systemic amyloidosis: 10 AL-CMP patients, 20 patients with TTR-associated forms of cardiac amyloidosis, ie, senile systemic amyloidosis (involving wild-type TTR) or mutant TTR, and 10 patients with AL amyloidosis without cardiac involvement. Serum MMP-2 and -9, TIMP-1, -2, and -4, brain natriuretic peptide values, and echocardiography were determined. AL-CMP and TTR-related amyloidosis groups had similar degrees of increased left ventricular wall thickness. However, brain natriuretic peptide, MMP-9, and TIMP-1 levels were distinctly elevated accompanied by marked diastolic dysfunction in the AL-CMP group versus no or minimal increases in the TTR-related amyloidosis group. Brain natriuretic peptide, MMPs, and TIMPs were not correlated with the degree of left ventricular wall thickness but were correlated to each other and to measures of diastolic dysfunction. Immunostaining of human endomyocardial biopsies showed diffuse expression of MMP-9 and TIMP-1 in AL-CMP and limited expression in TTR-related amyloidosis hearts.

Conclusions—Despite comparable left ventricular wall thickness with TTR-related cardiac amyloidosis, AL-CMP patients have higher brain natriuretic peptide, MMPs, and TIMPs, which correlated with diastolic dysfunction. These findings suggest a relationship between light chains and extracellular matrix proteolytic activation that may play an important role in the functional and clinical manifestations of AL-CMP, distinct from the other non–light chain cardiac amyloidoses. (Circ Heart Fail. 2008;1:249-257.)

Key Words: amyloid ■ cardiomyopathy ■ metalloproteinases ■ remodeling ■ immunoglobulin light chains

Cardiac amyloidosis, a rare disorder, is characterized by amyloid fibril deposition in the heart, resulting in a restrictive cardiomyopathy that manifests late with heart failure (HF) and conduction abnormalities.1–3 Amyloid infiltration leads to extracellular matrix (ECM) disruption resulting in diastolic dysfunction from progressive thickening and stiffening of the myocardium.1,4 There are several types of cardiac amyloidoses, which are classified according to the biochemical nature of the amyloid deposit. In “primary” or immunoglobulin light chain amyloidosis (AL), fibrils are formed from aggregated subunits (or fragments thereof) of an amyloidogenic monoclonal light chain protein.5 Transthyretin (TTR), normally a plasma-circulating protein, can also form amyloid deposits in myocardial tissue. Wild-type TTR is responsible for the cardiomyopathy in age-related senile systemic amyloidosis (SSA). Heritable mutations in TTR (ATTR) can result in cardiac or neuronal deposition of amyloid protein.3,6 Of these disease types, AL-cardiac amy-
Amyloidosis (AL-CMP) has the worse prognosis, an aspect that is seemingly disproportionate to the structural involvement of the amyloid fibril infiltration in the myocardium. A partial explanation may lie in studies, which demonstrate that light chains derived from patients with AL-CMP have direct effects on cardiomyocyte function, exerting negative inotropic effects and impairing excitation contraction coupling via increased oxidative stress.

An alternative/complementary explanation that has not to our knowledge been explored is whether AL versus TTR amyloid fibrils differentially alters ECM turnover, a critical process in the heart for proper maintenance of myocyte–myocyte force coupling and proper myocardial function. Therefore, extracellular amyloid fibrils have a high likelihood of disrupting the matrix homeostasis. Matrix homeostasis and composition are determined, in part, by collagen degradation, which are under the control of matrix metalloproteinases (MMPs), a family of zinc-dependent interstitial enzymes, and their tissue inhibitors (TIMPs). In nonamyloid cardiomyopathy, circulating MMPs and TIMPs are associated with progressive myocardial remodeling and dysfunction. We hypothesized that light chain amyloid deposition in the heart would alter the ECM homeostasis, activate the degradation system, and thus contribute to the pathogenesis of AL-CMP, whereas other forms of cardiac amyloid would result in less ECM activation. We tested this hypothesis indirectly by measuring circulating levels of selected MMPs and TIMPs in 3 patient groups: (1) AL-CMP, (2) cardiac amyloidosis due to wild-type TTR (SSA) or mutant TTR (ATTR), and (3) light chain amyloidosis featuring renal disease without cardiac involvement (AL-renal).

**Methods**

**Patient Data Collection**

Forty age-matched patients for whom echocardiographic data and serum samples were available were selected for study, based on amyloid type. Clinical and laboratory evaluations were performed in the Amyloid Treatment and Research Program at Boston Medical Center, between November 2003 and April 2007. All subjects consented to participate in a research study under a protocol approved by the Boston University Medical Center Institutional Review Board. Subjects had biopsy-proven amyloidosis confirmed by positive Congo red staining of tissue specimens. Subjects underwent a medical history and physical examination, routine laboratory tests (eg, electrolytes, brain natriuretic peptide [BNP], blood count), 24-hour urine collection, 12-lead electrocardiography, chest x-ray examination, and echocardiography with Doppler study. AL amyloidosis is associated with a plasma cell dyscrasia and typical findings include the production of a clonal immunoglobulin light chain in the bone marrow with the presence of light chain in the serum and/or urine. Therefore, all patients were evaluated for a plasma cell dyscrasia by serum and urine immunofixation electrophoresis and by bone marrow biopsy with immunohistochemical examination to determine the presence of a monoclonal population of plasma cells.

Amyloid cardiac involvement was determined by a history of HF with myocardial wall thickening on echocardiogram (without a history of hypertension or valvular disease), low voltage on surface ECG or by an endomyocardial biopsy specimen that demonstrated amyloid deposits. Clinical HF was determined by history and physical examination followed by New York Heart Association functional classification of HF severity. AL amyloidosis was excluded if monoclonal plasma cells were absent in the bone marrow and no monoclonal gammopathy was detected in the serum or urine. Once AL amyloidosis was excluded, patients underwent screening for ATTR amyloidosis by isoelectric focusing of serum designed to detect the presence of mutant transthyretin.

Direct DNA sequencing of the TTR gene validated a positive focusing of serum designed to detect the presence of mutant transthyretin. Direct DNA sequencing of the TTR gene validated a positive focusing of serum designed to detect the presence of mutant transthyretin. Direct DNA sequencing of the TTR gene validated a positive focusing of serum designed to detect the presence of mutant transthyretin.

**Echocardiography**

Two-dimensional and Doppler echocardiography were performed at baseline as previously described using the Vingmed Vivid Five System (GE Vingmed, Milwaukee, Wis) with a 2.5-MHz phased-array transducer. Echocardiograms were performed and analyzed in a blinded manner. Measurements of systolic and diastolic chamber dimensions and wall thickness were obtained from 2D imaging according to the recommendations of the American Society of Echocardiography. Left ventricular wall thickness (LVWT) is derived from an average of the interventricular septum and posterior wall thickness. Left ventricular (LV) mass was derived from the formula described by Devereux et al 2D echocardiographic data were analyzed for LV size and function and myocardial characteristics. Adequate Doppler tracings were available for all patients. Left ventricular end-diastolic and end-systolic volumes were calculated from 2D echocardiographic dimensions as previously validated: end-diastolic volume = 4.5 (LV diastolic dimension)² and end-systolic volume = 3.72 (LV systolic dimension)². These measurements are reliable only in subjects without a regional wall motion, ie, only validated in symmetrically contracting ventricles with normal ejection fraction. From these volumes, stroke volume was estimated as end-diastolic volume − end-systolic volume. Cardiac output was calculated as stroke volume/heart rate. Similarly, relative wall thickness was calculated as (2/posterior wall thickness)/left ventricle end-diastolic diameter. Transmitral Doppler LV filling recordings were performed from the apical 4-chamber view and analyzed for diastolic filling indexes, including peak E- and A-wave velocities and their ratio. Tissue Doppler imaging was used to determine the myocardial velocity of the mitral annulus to derive e′-prime (e′).

**Biomarker Analysis**

Blood samples were obtained at the first visit to the Amyloid Treatment and Research Program, before initiation of treatment. BNP values were measured, using the ADVIA Centaur assay (Siemens Healthcare Diagnostics), immediately after blood collection as part of routine laboratory testing. Serum samples were kept at −80°C for other assays. Gelatinases (MMP-2 and MMP-9) and tissue inhibitors of MMPs (TIMP-1, TIMP-2) were measured with commercially available ELISA kits from Amersham Pharmacia Biotech. (Buckinghamshire, United Kingdom) and the TIMP-4 kit from R&D Systems (Minneapolis, Minn).

**Endomyocardial Biopsies**

Myocardial tissue samples were obtained from the right ventricular septal endomyocardium, in subjects in whom the diagnosis of cardiac amyloidosis needed to be made (6 to 8 samples for each patient). This was performed from the right internal jugular vein with the use of combined fluoroscopic and echocardiographic guidance. Samples were placed in room temperature in a fixative (10% neutral buffered formalin) with a sterile needle. Endomyocardial biopsy tissue was embedded in paraffin and serial sections obtained. Congo red staining was performed on 4 to 6 μm sections to confirm amyloidosis. The remaining slides were preserved for immunohistochemistry.

**Immunohistochemistry**

Paraffin sections were deparaffinized, hydrated, and blocked with hydrogen peroxide for 10 minutes. The sections were then rinsed 3 times in Tween (0.05%) Tris (0.05 mol/L) buffer solution (TBTS, DakoCytomation, Glostrup, Denmark) before applying the primary antibody. Anti-MMP-9 was diluted (1:25) in antibody diluent from Dako and anti-TIMP-1 was diluted (1:50) in antibody diluent from Dako from a stock of 500 μg/mL (R&D Systems, Minneapolis, Minn). Tissue sections and antibodies were incubated overnight at 4°C, rinsed 3 times in TBTS, and incubated in HRP-labeled polymer.
(DakoCytomation, Glostrup, Denmark) for 30 minutes. They were then rinsed with TTBS, treated with diaminobenzidine for 5 minutes, rinsed 3 times with ddH2O, and counterstained in Harris hematoxylin for 30 seconds. After counterstaining, sections were rinsed with H2O for 5 minutes, dipped twice in 0.25% acid alcohol, briefly rinsed in H2O, and placed into 1% ammonia for 10 to 20 seconds before dehydrating and mounting the slides. Sections were visualized under bright-field microscopy and images were recorded using an Optronics camera with Bioquant Image software.

**Statistical Analysis**

Continuous variables are described as mean ± standard error or median (interquartile range). Categorical variables are described as number of patients and percentages. Differences between all 3 groups regarding echocardiography characteristics, BNP, MMPs, and TIMPs were determined using ANOVA and Turkey multiple-comparison post hoc tests, or Kruskal-Wallis test for nonnormally distributed variables. Spearman correlation test was used to evaluate the correlation between echocardiographic parameters, hemodynamics, BNP, MMPs, and TIMPs. All analyses were conducted using SPSS software, version 11.5 (SPSS Inc, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Patient Characteristics**

Forty patients were included in the study: 10 AL-CMP patients, 20 patients with cardiac amyloidosis due to wild-type TTR (SSA) or ATTR, and 10 patients with AL amyloidosis featuring renal disease without cardiac involvement (AL-renal). One hundred percent of patients were white in AL-CMP, 75% in SSA-ATTR, and 80% in AL-renal. Additional clinical characteristics for each group are shown in Table 1. Age, body surface area, and body mass index were similar among all groups. Most of the patients were male. Systolic blood pressure was lowest in the AL-CMP group, but within the normal range. Serum free light chain measurements, revealed a predominance of k over λ in AL-CMP and AL-renal. In the SSA-ATTR group, patients had a normal serum and urine profile. Renal function was most impaired in the AL-renal group. Almost all patients with cardiac amyloidosis (AL-CMP and SSA-ATTR) had clinical HF symptoms. Many of these patients had severe cardiac thickening and evidence of systolic and diastolic dysfunction.

**LV Size, Structure, and Function**

The echocardiographic data for all groups is shown in Table 2. The LV mass was significantly higher in the AL-CMP and SSA-ATTR groups when compared with AL-renal group, which had no pathological LVWT. Both AL-CMP and SSA-ATTR groups had marked and comparable LVWT and concentric hypertrophy. The average calculated end-systolic volume was slightly increased in the SSA-ATTR group, demonstrating that non–light chain deposition in the heart is associated with slight LV dilation.
In the AL-CMP and SSA-ATTR groups, LV fractional shortening and calculated ejection fraction were significantly lower and in the “mildly abnormal” range. Calculated stroke volume, cardiac output, and cardiac index were all decreased in AL-CMP versus AL-renal and SSA-ATTR, reflecting impaired hemodynamics with light chain amyloid deposition. There was evidence of diastolic dysfunction in both AL-CMP and SSA-ATTR (increased E/A ratio and lower early diastolic mitral annular motion [e’] velocity). The E/e’ ratio revealed that left atrial (LA) pressure was significantly higher in AL-CMP.

### BNP and ECM Proteolytic Marker Profile

Despite a comparable degree of increased cardiac wall thickness in the AL-CMP and SSA-ATTR groups, AL-CMP patients showed a marked increase in BNP values (231±773 ng/mL, compared with a modest increase observed in the SSA-ATTR group (360±53 ng/mL; \( P<0.01 \); Figure 1A). Likewise, TIMP-1 values were increased in AL-CMP (1161±90 ng/mL) versus AL-renal (876±53 ng/mL; \( P=0.01 \)) and SSA-ATTR (912±67 ng/mL; \( P=0.05 \); Figure 1B). In contrast, MMP-9 levels were significantly increased in both AL groups (23±6 ng/mL for AL-CMP, 18±3 ng/mL for AL-renal) versus the SSA-ATTR group (10±1 ng/mL; \( P<0.05 \) versus AL-CMP and AL-renal; Figure 1C). The other markers, TIMP-2, TIMP-4 and MMP-2, were not significantly altered in any of the 3 groups (Figures 1D through 1F).

Despite a similar clinical course and the lack of light chains in SSA and ATTR cardiac amyloidoses, there is evidence that the mechanism for amyloid deposition in SSA and ATTR may differ.21 We compared whether the ECM proteolytic system and BNP levels differed between SSA and ATTR groups. BNP, TIMP-1, TIMP-2, TIMP-4, and MMP-2 were similar between the 2 groups, whereas MMP-9 levels were higher in the SSA (13±6.2 ng/mL) versus the ATTR group (7±2.4 ng/mL; \( P=0.02 \)). Both set of values were significantly lower than those in the AL-CMP group (23±6 ng/mL).

### Correlations Between Measures of the ECM Proteolytic System, BNP, and Echocardiographically Derived Measures of Cardiac Remodeling

We further evaluated whether we could correlate the degree of LVWT and LV mass and functional impairment to serum BNP and markers of the ECM proteolytic system in patients with cardiac amyloid disease (n=30). There were no significant correlations between LV mass or LVWT to BNP, MMPs, and TIMPs. Because BNP is increased in cardiac amyloidosis and may reflect cardiomyocyte damage/toxicity, we further evaluated if BNP levels were correlated to ECM proteolytic activation. As shown in Figures 2A through 2D, there was a positive correlation between BNP levels and MMP-9, TIMP-1, MMP-2 levels and the ratio of MMP-9/TIMP-1.

Diastolic function was impaired in both AL-CMP and SSA-ATTR (Table 2). Interestingly, we found a significant negative correlation with e’ lateral tissue Doppler and BNP, TIMP-1, and MMP-9 (Figures 3A through 3C).

### Myocardial Biopsy MMP-9 and TIMP-1 Analyses

The presence and abundance of myocardial MMP-9 and TIMP-1 expression from patients with cardiac amyloidosis were investigated in endomyocardial biopsies (Figures 4A through 4C). MMP-9 expression was diffusely increased in AL-CMP (n=5) cardiomyocytes versus sparse expression in non–light chain cardiac amyloidosis (SSA; n=4). In AL-CMP, MMP-9 was visibly absent from the ECM (interstitium), which has been replaced by light chain amyloid deposits. In addition, there was scant MMP-9 expression in the perivascular areas. Likewise, TIMP-1 expression (Figure 4C) was

<table>
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<th>Table 2. Echocardiography Data</th>
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<tr>
<td>AL-Renal</td>
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<tr>
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<td><strong>LA pressure</strong></td>
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<td>E/e’</td>
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Data are presented as mean±SE. RWT indicates relative wall thickness; EDD, end-diastolic diameter; ESD, end-systolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; DT, deceleration time; IVRT, isovolumic relaxation time.

*\( P<0.05 \) versus AL-renal.
†\( P<0.05 \) versus AL-CMP.
increased in cardiomyocytes and also distributed diffusely throughout the myocardium in AL-CMP versus SSA hearts.

**Discussion**

This is the first study to evaluate the ECM proteolytic system in different forms of cardiac amyloidosis. Both light chain (AL-CMP) and non–light chain (SSA-ATTR) cardiac amyloidosis resulted in an increased but comparable LVWT and an increase in LV mass. Despite this structural similarity, the presence of cardiotropic amyloidogenic light chains resulted in distinct increases in serum concentrations of BNP, MMP-9, and TIMP-1, which correlated with measures of diastolic dysfunction in AL-CMP. Similarly, increased MMP-9 and TIMP-1 were present in myocardial tissue containing light chain amyloid deposits. These findings suggest a relationship between light chain-amyloid disease and ECM proteolytic activation, which might play a role in the progression of cardiac amyloid disease and the distinct differences in prognosis between these groups of patients.

**BNP Levels**

In cardiac amyloidosis, BNP is released from cardiomyocytes and there is direct evidence of an increase in BNP gene and protein expression in ventricular myocytes. The inactive proform of BNP, NT-proBNP, is elevated in AL-CMP and appears to precede overt cardiac involvement. Furthermore, BNP values have been shown to correlate with prognosis and response to therapy. In patients with cardiac...
disease and no amyloid, a good correlation exists between BNP and LVWT, diastolic dysfunction and end-diastolic wall stress. In our study, an interesting finding was that the highest BNP levels were present in the AL-CMP group, despite the fact that the SSA-ATTR group had similar cardiac mass, LVWT and severe diastolic dysfunction. Taken together, these findings suggest that increased BNP in cardiac amyloidosis may reflect not only elevated LV filling pressure, but also the direct cardiac myocyte damage due to extracellular deposition of light chains in AL-CMP.

There appears to be a paradoxical relationship between LA size and E/e' in AL-CMP versus SSA-ATTR groups. The greater LA size but lower E/e' in SSA-ATTR could be explained by a longer duration of cardiac disease, because LA enlargement is a marker of severity and the chronicity of diastolic dysfunction and the magnitude of LA pressure.

Figure 3. The relationship between tissue Doppler e' and BNP (A), TIMP-1 (B), and MMP-9 (C). Closed squares indicate AL-CMP; open squares, SSA-ATTR group.

Figure 4. Immunohistochemical analyses of MMP-9 and TIMP-1 in amyloidotic endomyocardial biopsy. A, There is no MMP-9 staining in the normal, nonamyloid heart. MMP-9 expression is more diffuse in AL-CMP than SSA heart biopsies. Solid blue arrows indicate amorphous amyloid deposition in the ECM. (Magnification ×100.) B, MMP-9 expression in AL-CMP and SSA heart biopsies. Solid black arrows indicate staining in cardiomyocytes; dashed back arrows, MMP-9 staining in the interstitium; red arrows, MMP-9 expression in (+) control; blue arrows, amyloid deposits in the ECM. (Magnification ×400.) C, TIMP-1 expression is more diffuse in AL-CMP than SSA heart biopsies. Solid arrows indicate TIMP-1 staining in cardiomyocytes; dashed arrows, TIMP-1 staining in the interstitium; red arrows, TIMP-1 expression in (+) control; blue arrows, amyloid deposition in the ECM. (Magnification ×400.)
The present study has several limitations. First, because this is a cross-sectional analysis, it does not allow conclusions regarding cause and effect. Further insight into the role of MMPs and TIMPs in depositions cardiac amyloidoses might be gained by intervention studies and longitudinal follow-up of patients with cardiac amyloidosis. Second, the sample size is relatively small and it is possible that relationships between BNP and other biomarkers (MMP-2, TIMP-1, and TIMP-4) would be observed in a larger group of subjects. However, our significant findings in this small sample size of patients may serve to highlight the role of these markers. In addition, other MMP and TIMP species are expressed within the human myocardium but only MMP-2, -9, TIMP-1, -2, and -4 levels were examined in the current study. Third, although AL amyloidosis is a systemic disease and we measured circulating biomarker levels, renal dysfunction could impact those levels, resulting in false-positive findings. However, there was no correlation between renal dysfunction, defined as the presence/absence of renal involvement or as creatinine levels, to BNP levels or ECM proteolytic markers, except for MMP-9, which was increased in both AL groups (data not shown). Moreover, a direct assessment of tissue MMP activity (ie, zymography) was not performed. Given our positive findings, further studies are required to identify other MMPs and TIMPs that may be altered in AL-CMP patients. Finally, differences in medication that can affect fibrosis across the 3 groups may be a potential limitation. However, most patients with cardiac amyloidosis were on minimal cardiac medications, and there were no differences in the distribution of the types of medications between the 3 groups of patients.

In conclusion, our study demonstrates that light chain cardiac amyloidosis, despite its structural similarities to other forms of cardiac amyloidosis (SSA or ATTR), results in disproportionate and markedly increased levels of BNP and ECM proteolytic markers, as well as impaired hemodynamics and diastolic dysfunction. These findings may provide insight into the mechanisms for accelerated amyloid disease progression and impaired prognosis associated with light chain cardiac involvement. Future studies will determine whether interventions aimed to interrupt this process may benefit this group of patients.

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Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Cardiac amyloidosis is characterized by amyloid fibril deposition in the heart with extracellular matrix disruption and progressive wall thickening and stiffening, resulting in a restrictive cardiomyopathy. Systemic amyloidosis featuring cardiac involvement (AL-CMP) is caused by immunoglobulin light chain protein deposition in the heart that may manifest with congestive heart failure, arrhythmias, and death within 6 months, if untreated. Although cardiac amyloidosis may be related to other non–light chain proteins (ie, amyloidosis associated with either wild-type transthyretin or a mutant transthyretin), the prognosis for patients with AL-CMP is worse and the mechanism poorly understood. Direct cardiotoxicity from light chains has been implicated. The current study shows that despite similar structural myocardial involvement (wall thickening and diastolic dysfunction) for both AL amyloidosis and the transthyretin-related forms, AL-CMP patients had higher brain natriuretic petide levels and increased markers of extracellular matrix proteolytic activity (MMP-9 and TIMP-1), which were not associated with the degree of wall thickening. Therefore, structural abnormalities by echocardiography may not reflect the severity of AL-CMP. The presence of light chains in AL-CMP, as well as increased levels of brain natriuretic petide and markers of extracellular matrix proteolytic activity, may reflect additional mechanisms that contribute to the accelerated clinical disease that has been reported. Our findings represent an initial step to increasing our understanding of the pathophysiology of this poorly understood disease. Subsequent steps would focus on the association of these markers with clinical course and prognosis and whether interventions directed to interrupt these processes would prevent disease progression and improve clinical outcome.
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