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Proteoglycans and Other Basement Membrane Proteins in Amyloidoses

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Index Entries: Amyloidosis; perlecan; laminin; fibronectin; collagen-IV Alzheimer's; AA; Aβ; basement membranes; binding.

Heparan sulfate (HS) or other highly sulfated glycosaminoglycans (GAGs) of the HS type have been shown to be constituents of every amyloid so far examined *(1)*. In inflammation-associated amyloidosis (AA-amyloid), HS, as part of the proteoglycan called perlecan, is deposited coincidentally with and causes serum amyloid A_2(SAA_2), the specific precursor of AA-amyloid, to take on significantly increased β-sheet conformation *(2–6)*. This effect is not seen with SAA_1, a closely related homolog, or with other GAGs *(6)*. Perlecan is an integral component of AA-amyloid fibrils *(5)*, and sulfate ions play a role in maintaining AA fibril structure *(7)*. Other basement proteins, in addition to perlecan, are deposited, coincidentally with SAA *(4)*. Upregulation of perlecan and collagen-α_1(IV) mRNA occurs prior to AA-amyloid deposition, and only in those animals receiving the full amyloid induction protocol *(8)*. Furthermore, SAA binds to laminin with high affinity, a process that competes with entactin binding to laminin *(9)*. This latter step is known to be necessary in the assembly of structural basement membranes *(10–12)*.

Significant parallels exist between AA-amyloid deposition and several other amyloids, including Alzheimer's amyloid (Aβ) deposits. Perlecan, collagen IV, laminin, and fibronectin are part of Aβ amyloid deposits *(13–15)*. Perlecan is a component of Aβ amyloid fibrils *(16,17)*. Recent studies by Fraser et al. have pointed out the significant influence of sulfate ions and heparin on the axial and lateral aggregation of β-peptides into Aβ fibrils *(18)*. A carbohydrate environment, such as that provided by micelles of octyl glucopyranoside, plays a role in altering the conformation of the β-peptide from an α-helical to a β-sheet configuration *(19)*. Upregulation of laminin mRNA occurs in the brains of Alzheimer's patients, but not in age-matched controls *(20)*. βPPs bind to perlecan and laminin with high affinity *(21–24)*, and can exert disruptive influences on basement-membrane protein interactions in much the same way that SAA interferes with laminin:entactin binding *(25)*. The binding of perlecan to βPPs is influenced by its GAG side chain *(21)*, and at least one binding site is on the β-peptide itself *(18)*.

These parallels suggest that the process of amyloidogenesis in these two disorders, AA and Aβ amyloid, is similar, and that basement-membrane components are integral players in the genesis of amyloidoses. They further suggest that the failure to form basement membranes at sites of amyloid formation, although all the necessary basement-membrane proteins are present, may well represent the opposite face of the same metabolic process. Viewed from one perspective, basement-membrane protein binding to an amyloid precursor (or peptide) may influence the protein with amyloidogenic potential to commence the process of amyloid deposition. Viewed from the other, the amyloid pre-

cursor (or peptide) on interacting with basement membrane proteins, which are not yet integrated structurally into a basement membrane, precludes these proteins from forming basement membranes, a process in which they would spontaneously engage in the absence of an amyloidogenic protein *(26)*.

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