Molecular Neurobiology

ISSN0893-7648/94/8(1): 65–66/$3.00

Inflammation-Associated Amyloidogenesis

Lessons for Alzheimer's Amyloidogenesis

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Index Entries: Amyloidosis; AA; inflammation; SAA; AEF; Alzheimer's disease; basement membrane proteins; HDL.

Inflammation-associated amyloid (AA amyloid) occurs clinically and experimentally in a setting of persistent acute inflammation. AA amyloidogenesis is the only model now available where amyloid deposition can be consciously manipulated.

A review of the factors responsible for the induction of serum amyloid A (SAA, the precursor to AA deposits) synthesis by the liver and a consideration of the in vivo microenvironmental conditions under which SAA is converted to an amyloid deposit indicate that during an inflammatory reaction two processes occur that are relevant to AA amyloid deposition. The first concerns the process by which liver SAA synthesis is upregulated, and the second concerns the process by which SAA metabolism is altered.

With regard to the first, any inflammatory stimulus leads to the activation of inflammatory cells, such as macrophages, which secrete cytokines, such as IL-1, IL-6, and tumor necrosis factor *(1–4)*. These cytokines, in conjunction with specific nuclear factors *(5–8)*, upregulate the expression of a set of acute-phase protein genes among which are those for SAA. Elevated serum levels of SAA are seen 4–6 h following an inflammatory stimulus *(9)* and reach levels 500–1000-fold above the noninflammatory state in 15–20 h *(9–11)*. The presence of the AA amyloid precursor at such high levels has been shown to be insufficient, on its own, to cause amyloid deposits *(9)*. In the circulation, SAA is bound primarily to high-density lipoprotein (HDL) *(12,13)*. SAA apparently serves as an address for HDL, redirecting this reverse cholesterol transporter, to bind to cells of the reticulo-endothelial series during inflammation *(14)*. This process takes SAA to its site of potential deposition.

The second process concerns the appearance, in tissues about to deposit AA amyloid, of a factor that has been termed amyloid-enhancing factor (AEF) *(15,16)*. AEF is probably a glycoprotein, although its precise nature has not yet been identified *(16)*. It has been shown convincingly that in the presence of AEF, SAA is mishandled metabolically *(17)* and is deposited as AA amyloid, a process that takes as little as 36 h *(16)*. Preliminary evidence suggests that AEF may effect a change in basement membrane metabolism that appears crucial for amyloidogenesis *(18)*. Upregulation of the mRNAs for the

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heparan sulfate proteoglycan perlecan and collagen-α_1 (IV) precede amyloid deposition, and only in those animals receiving the complete amyloid induction protocol *(19)*. Furthermore, proteolysis of SAA does not appear to be necessary for AA amyloid formation *(20)*. Rather, its interaction with basement membrane proteins, which have yet to be incorporated into a structural basement membrane, may lead to the alteration in SAA's secondary or tertiary structure characteristic of an amyloid deposit *(21)*. As part of the same process, there is disruption of basement membrane formation.

Significant parallels between AA amyloid and Alzheimer's (Aβ) amyloid exist. Upregulation of the genes for each precursor occurs in the corresponding conditions. AEF has been identified in both situations *(15,16,22)*. Upregulation of genes for basement membrane proteins has been demonstrated in each case *(23,24)*. Basement membrane proteins are constituents of each deposit *(25–27)*, bind to each precursor with high affinity *(28–30)*, and can effect configurational changes in the conformations of the relevant precursors that correspond to those seen in amyloid deposits *(21,31)*. Proteolysis, which appears to be unnecessary in many forms of amyloid *(32)*, may not be as critical an event in Aβ as is now believed.

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