

Altered distribution of AA amyloid pathology in immunocompromized mice: A quantitative SPECT imaging study

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Amyloidosis is a protein-folding disorder characterized by the aggregation and deposition of proteinaceous fibrils in vital organs and tissues. The most common form of non-cerebral amyloidosis Worldwide and the second most prevalent form of peripheral amyloidosis in the USA is reactive (AA) amyloidosis which is associated with chronic inflammatory disorders such as arthritis and tuberculosis. The incidence of AA in US patients with rheumatoid or psoriatic arthritis can be as high as 26%.

Effective translation of novel therapeutic and diagnostic agents for AA requires a tractable animal model that reliably recapitulates human pathology. In this regard, the experimental murine model of systemic AA amyloidosis provides reproducible, controllable amyloid deposition involving multiple organs. We have used these mice to study novel immunotherapeutic approaches for the treatment of AA amyloidosis. In particular, we have shown that AA amyloidosis induced in transgenic H2-L^d-huL-6 Tg Balb/c (C) mice could be alleviated by multiple infusions of a fibril-reactive murine monoclonal antibody (mAb), designated 11-1F4. Furthermore, AA deposition was completely prevented by prophylactic mAb administration.

Through the RAID Program at the National Cancer Institute we now have a chimeric (c) form of mAb 11-1F4 for study. This necessitates the use immunocompromized mice with AA amyloidosis. Therefore, AA has been induced in scid [CB17/Icr.Cg-Prkdc^{scid} Lyst^{tg}/Crl] and Rag1-/- [C.129S7(B6)-Rag1^{tm1Mom}/J] mice by injecting pro-inflammatory silver nitrate solution and amyloid enhancing factor. AA deposits were detected in both strains of mice as evidenced histologically and in SPECT images using ¹²⁵I-labeled serum amyloid P component as a tracer. Remarkably, the distribution of the amyloid differed in the immunocompromized strains as compared to similarly treated Balb/c mice. Hepatic amyloid was greater in the scid and Rag1-/- mice, retaining ~ 40 – 50% ID/g of ¹²⁵I-SAP at 24 h post-injection as compared to ~ 20% in Balb/c mice. In contrast, scant splenic AA was seen in the scid and Rag1-/- mice (< 10% ID/g) as compared to ~ 50% ID/g in the Balb/c. These biodistribution data correlated with the mean voxel intensity values obtained from SPECT images.

The studies demonstrate that AA amyloidosis can be induced in immunocompromized mice but the distribution of the AA deposits induced in scid and Rag1-/- mice differs from that in Balb/c mice, possibly due to the to the lack of functional lymphocytes or follicular integrity in the spleen.