A TRANSGENIC MOUSE LINE EXPRESSING AN AMYLOIDOGENIC HUMAN TRANSTHYRETIN

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ABSTRACT

Amyloidosis is a group of conditions characterized by the deposition of insoluble protein fibrils. Deposits can occur either locally or systemically, depending on the protein involved. Systemic amyloidosis may occur sporadically (Immunoglobulin, AL), secondary to inflammatory disease (Reactive, AA) or in an inherited fashion (Hereditary, AH). Hereditary amyloidosis, also known as Familial Amyloidotic Polyneuropathy (FAP), is transmitted as an autosomal dominant trait. In most of the hereditary forms the amyloid protein has been identified as transthyretin (TTR), a plasma protein. Most of the known cases of transthyretin amyloidosis result from variant proteins containing a single amino acid substitution. Other proteins, such as apolipoprotein AI, gelsolin, fibrinogen, cystatin C and lysozyme have been shown to cause systemic amyloid deposits in some kindreds as well. While much has been discovered about the molecular and biochemical basis of hereditary amyloidosis in recent years, the basic mechanism of amyloid formation remains a mystery. As a result, the current treatment of this condition involves minimizing the damage caused by the amyloid, with liver transplantation the only means of preventing the accumulation of further deposits for those proteins synthesized by the liver. Since hereditary amyloidosis is strictly a disease of humans, research on pathogenesis has been hampered by the lack of a suitable animal model. The main objective of this research is the development of a transgenic mouse line expressing an

amyloidogenic human transthyretin gene.

The initial step involved isolating a full-length variant TTR gene from an affected individual. The intact mutant gene, along with upstream sequence, was cloned and used to create several lines of transgenic mice by the pronucleus microinjection technique. Several of these lines demonstrated high expression levels of variant human TTR in their serum and subsequent breedings confirmed transmission of the transgene. The pattern of expression of the transgene in various tissues in the mouse was found to parallel the known pattern of expression in humans. This suggests that regulatory sequences in the upstream region of the transgene are appropriately controlling expression in the mouse.

Histopathological examination of representative members of each line was conducted at regular intervals for evidence of amyloid formation. Two animals have developed amyloid deposits composed of serum amyloid A protein, but no transthyretin amyloid was seen. Even without evidence of transthyretin amyloid formation, this animal model serves a useful role in basic research in finding a cure for this debilitating condition.

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