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Hereditary transthyretin amyloidosis: molecular basis and therapeutical strategies

Maria João Mascarenhas Saraiva

Transthyretin (TTR) is a transport protein for thyroid hormones and vitamin A and might have an important role in the nervous system. However, TTR can undergo a conformational change and form amyloid fibrils, in both acquired and hereditary forms of systemic amyloidosis. More than 80 TTR mutations have been associated with autosomal dominant amyloidosis, usually presenting with peripheral and autonomic neuropathy and/or cardiomyopathy. Major areas of research in TTR amyloidosis include: molecular mechanisms leading to fibril formation; mechanisms of fibril-induced cell death; modulators of phenotypic expression of the disease; and therapeutic strategies.

The amyloidoses comprise a spectrum of acquired and hereditary diseases caused by the deposition of characteristic fibrillar material in various organs and tissues throughout the body. These fibrils are 7–10 nm wide, rigid and non-branching (Fig. 1a), and are of variable length with a common twisted β-pleated-sheet structure (Ref. 1). They have unique tinctorial properties, including apple-green birefringence when viewed under polarised light after staining with Congo red (Fig. 1b). Amyloid fibril accumulation ultimately damages the structure and function of affected organs.

Systems based on clinical phenotypes have historically been used to classify the amyloidoses, but emphasis is now placed on characterisation of the amyloid fibril protein. For example, AL amyloidosis, formerly known as primary amyloidosis, is caused by the accumulation of monoclonal immunoglobulin (Ig) light chains as amyloid fibrils (Ref. 2). Igs are synthesised by plasma cells and are usually maintained at a balanced level; however, in AL amyloidosis, clonal plasma cells express Ig light chains with amyloidogenic potential – that is, chains that can polymerise as amyloid fibrils in multiple organs of the body, including kidney, heart, liver, intestines, skin, spleen and lungs. As these deposits build up, they begin to affect organ function. This disease affects men and women, with a peak occurrence at 60–65 years, but even quite young adults can be affected.

Systemic AA amyloidosis is associated with chronic inflammatory diseases (e.g. rheumatoid arthritis) and involves amyloid deposition in organs such as the kidneys, liver and spleen (Ref. 3), in which the fibrils are derived from the circulating acute-phase reactant serum amyloid A protein.

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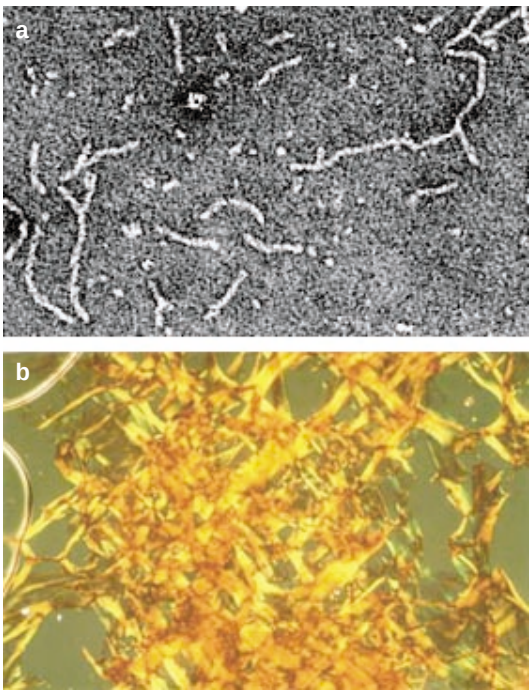

Features of amyloid fibrils

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Figure 1. Features of amyloid fibrils. (a) Electron microscopy of amyloid fibrils. The fibrils are 7–10 nm wide, rigid and non-branching. Magnification, X30 000. (b) Amyloid fibrils show unique tinctorial properties, such as apple-green birefringence under polarised light upon staining with Congo red. Magnification, X30 **(fig001msp)**.

Hereditary transthyretin (TTR) amyloidosis is a genetically transmitted disease that results from a mutation in the gene encoding the plasma TTR protein (Ref. 4). TTR is a transport protein for thyroid hormones and vitamin A [in the case of vitamin A (retinol) this is via formation of a complex with retinol-binding protein] and is predominantly synthesised in the liver. Although hereditary TTR amyloidosis was originally regarded as a rare disease, it is now becoming clear that many kindreds exist worldwide. The mechanisms by which the various TTR mutations lead to amyloid aggregation, and the pathogenic consequences of this, have been the focus of research for two decades. This review summarises current knowledge and hypotheses on the biology and genetics of TTR, mechanisms of TTR amyloid fibril formation, and the phenotypic consequences of TTR amyloid deposition. Finally, new avenues that might lead to prevention and therapy of TTR amyloidosis are examined.

The genetics of hereditary TTR amyloidosis

In 1952, Andrade identified the first form of hereditary amyloidosis – familial amyloidotic polyneuropathy (FAP) – in kindreds in the northern area of Portugal near Porto. The clinical symptoms began in the third to fourth decade of life; typical features were early impairment of temperature and pain sensation in the feet, and autonomic dysfunction leading to paresis, malabsorption, emaciation and death (Ref. 5). The genetic defect in these Portuguese FAP kindreds is heterozygosity for a single point mutation in TTR, giving rise to variant TTR Val30Met (substitution of valine by methionine at amino acid position 30) (Ref. 4). In the region of Portugal where FAP is common, the gene carrier frequency has been estimated to be 1 in 625 (Ref. 6). The TTR gene is located on chromosome 18 (Ref. 7) and is composed of four exons, each of approximately 200 bp (Ref. 8). The Val30Met variant results from a single point mutation in which guanine is substituted by adenine. This creates a restriction site for the enzyme *Nsi*I (Ref. 9), which facilitates the molecular diagnosis of TTR Val30Met FAP by restriction fragment length polymorphism (RFLP) analysis of polymerase chain reaction (PCR)-amplified DNA.

FAP kindreds with TTR Val30Met have subsequently been identified throughout the world, with particular foci in northern Sweden, Japan and Majorca (Refs 10, 11, 12). In addition, over 80 other TTR mutations have been identified throughout the TTR gene (http://www.ibmc.up.pt/~mjsaraiv/ttrmut.html). Some mutations are associated with FAP that is indistinguishable clinically from the original description of the disease; others give rise to phenotypes that variously include neuropathy, cardiomyopathy, carpal tunnel syndrome (entrapment of the median nerve at the carpal bones of the wrist), vitreous TTR deposition and leptomeningeal involvement.

A few TTR mutations are related predominantly to cardiomyopathy. The most common TTR mutation associated with cardiac amyloidosis is Val122Ile, described in the American black population. After the age of 60, apparently isolated cardiac amyloidosis is four

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times more common among blacks than whites in the USA, and 3.9% of blacks are heterozygous for Val122Ile (Ref. 13).

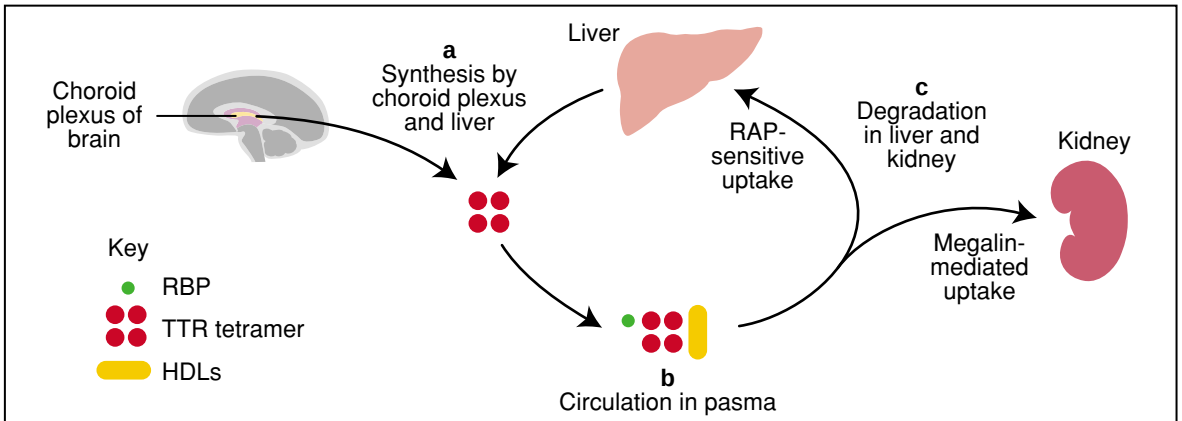
Susceptibility to amyloidosis is governed by heterozygosity for TTR mutations, which show autosomal dominant inheritance with variable penetrance. However, some TTR mutations appear to be non-amyloidogenic, and can be responsible for hyperthyroxinaemia (Ref. 14). In addition, compound heterozygotes have been identified, in whom two TTR mutations are present (Ref. 6).

Interestingly, in some cases where a pathogenic and a non-pathogenic mutation occur, the non-pathogenic mutation might protect against the development of FAP (Ref. 15). Normal wild-type TTR is itself weakly amyloidogenic and is deposited as amyloid predominantly in the hearts of up to 25% of elderly people, a condition termed senile systemic amyloidosis (Ref. 16).

TTR biology in health

TTR is a tetrameric serum protein of four identical subunits of 14 kDa, synthesised mainly in the liver and the choroid plexus of the brain (Ref. 17). Each monomer contains two β-sheets that interact to form a dimer. The molecular structure has been determined by X-ray analysis (Ref. 18), and amyloidogenic mutations appear to reduce the stability of the tetrameric structure (see discussion below).

Plasma TTR is derived mostly from the liver and acts as a transport protein for thyroxine and also vitamin A (Ref. 19); in the latter case, this is accomplished by the formation of a 1:1 molar complex with retinol-binding protein (Ref. 20) (Fig. 2). TTR binds virtually all of serum retinol-binding protein and about 15% of serum thyroxine. TTR is the main thyroxine transport protein in cerebrospinal fluid (CSF) and might contribute to the transport of serum thyroxine across the blood–brain and blood–choroid-plexus–CSF barriers (Ref. 21). However, although TTR-knockout mice have depressed levels of retinol and thyroxine, they have an otherwise normal phenotype; in particular, absence of TTR does not impair transport of thyroxine to the brain (Ref. 22) and does not produce measurable features of hypothyroidism, including effects on the brain parenchyma (Ref. 23). This questions the role of the protein in the transport of thyroxine from blood into the brain



Synthesis, circulation and uptake of transthyretin

Figure 2. Synthesis, circulation and uptake of transthyretin. (a) Transthyretin (TTR) tetramer (red circles) is synthesised by the choroid plexus of the brain and by the liver. The mechanisms underlying delivery and uptake of TTR within and out of the brain are not known. (b) The tetramer circulates in plasma bound to retinol-binding protein (RBP; green circle), thereby providing a transport function for vitamin A; and a small proportion of TTR binds high-density lipoproteins (HDLs; yellow bar). (c) TTR is degraded in kidney and liver, as well as muscle and skin (not shown). In the kidney tubules, TTR is taken up by megalin [a member of the low-density lipoprotein (LDL) receptor family]; in liver, an as yet unidentified receptor that binds receptor-associated protein (RAP) (a binding characteristic of LDL receptors) is responsible for TTR uptake **(fig002msp)**.

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(Fig. 2), although compensatory mechanisms for thyroxine metabolism might operate in the absence of TTR. An analagous situation arises in humans, when TTR mutations reduce the affinity of TTR for thyroxine. For example, TTR Val30Met homozygotes are euthyroid despite their TTR binding virtually no thyroxine (Ref. 24). TTR also binds other ligands such as pterins (Ref. 25) but the significance of this interaction is not yet known.

The liver, kidney, muscle and skin are thought to be major sites of TTR degradation in the rat (Ref. 26), but its cellular uptake is poorly understood. Specific and saturable TTR uptake, consistent with the existence of a receptor-mediated process, has been reported in hepatomas and ependymomas (Refs 27, 28). Vieira and colleagues (Ref. 29) have investigated the transport of serum TTR into chicken oocytes and demonstrated the existence of a ~115 kDa oocytic TTR receptor that might be responsible for regulating the uptake of thyroxine and retinol into the growing embryo.

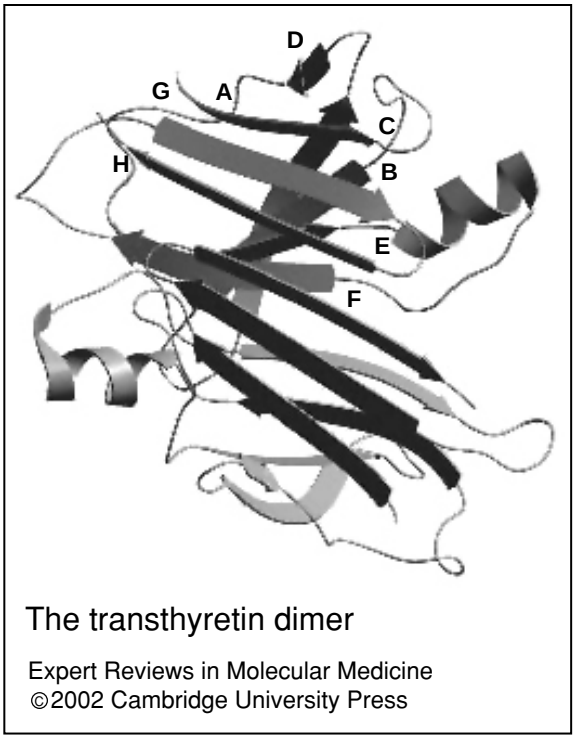
All these reports support a receptor-mediated process for TTR internalisation in several tissues but information is lacking on the biochemical nature of the TTR–receptor interaction. Approximately 1–2% of plasma TTR circulates bound to high-density lipoproteins (HDLs) and the association of TTR with the HDL vesicle occurs via apolipoprotein AI (apoAI) (Ref. 30). TTR uptake experiments using different cell lines and systems suggest a possible common pathway for lipoprotein and TTR uptake (Fig. 2). Thus, megalin, a member of the low-density lipoprotein (LDL) receptor family is a receptor for TTR uptake as demonstrated in vitro by cell lines expressing megalin and by surface plasmon resonance (SPR) analysis. Megalin-knockout mice excrete TTR and lack lysosomal accumulation of TTR in renal tubules, demonstrating the role of megalin in TTR uptake in kidney (Ref. 31). Furthermore, patients with renal tubular impairment excrete TTR (Ref. 31).

Members of the LDL receptor family have in common the ability to bind the receptor-associated protein (RAP), a protein that antagonises binding of ligands to this family of receptors (Ref. 32). In liver and other tissues, uptake of TTR was found to be inhibited by RAP and lipoproteins (Ref. 33). Further dissection of these mechanisms will help establish a possible link between TTR and lipoprotein metabolism.

Why does TTR aggregate as amyloid?

The precise mechanisms underlying TTR amyloid fibril formation are unknown, but the amyloidogenic potential of the protein might be related to its extensive β-sheet structure (Ref. 18). The two β-sheets in each monomer are composed of strands DAGH and CBEF, which interact face-to-face through hydrogen bonds between strands HH' and FF' to form a dimer (Fig. 3). In the tetramer, hydrogen bonds occur between main-chain atoms belonging to loop AB of one monomer and strand H' from the other monomer, in addition to hydrophobic contacts.

The effects introduced by amyloidogenic mutations have been the subject of intensive study, mainly by X-ray crystallography, and the solved structures indicate destabilisation of the tetrameric structure of the protein. Structural studies by X-ray diffraction on a particularly clinically aggressive mutant TTR (Leu55Pro) were



The transthyretin dimer

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Figure 3. The transthyretin dimer. Each monomer comprises two β-sheets formed by strands DAGH and CBEF, one α-helix and some disordered structure. The β-sheets interact face-to-face through hydrogen bonds between strands HH' and FF' to form the dimer. Disruption of the D strand affects hydrogen bonding with the A strand. This exposes new surfaces, which might be involved in aggregation **(fig003msp)**.

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performed on an aggregated 'amyloid-like' oligomer state of the protein, and revealed monomers as the building blocks of the structure (Ref. 34). Important changes were observed in secondary structure as a result of the disruption of strand D, which becomes part of a long loop that connects strands C and E (Ref. 34). Disruption of the D strand affects the hydrogen bonding with the A strand, exposing new surfaces involved in aggregation; in particular, the contacts of the α-helix and the AB loop are different, suggesting that these regions are important in stabilising the molecule. In fact, deletion or multiple substitutions in the D strand lead to highly amyloidogenic mutants (Ref. 35). The Leu55Pro structure also highlighted an important bond between Tyr78 and the AB loop that stabilises the quaternary structure. On the basis of this information, a putative amyloidogenic TTR mutant Tyr78Phe was constructed that formed fibrils readily at neutral pH (Ref. 36). This mutant was shown later to exist in vivo, in an Italian patient with late-onset severe amyloid cardiomyopathy (Ref. 37).

All of these structural studies have associated the amyloidogenic potential of TTR with weak interactions between its subunits. Indeed, stability studies have shown a relationship between the amyloidogenic potential of TTR and a decrease in tetrameric stability (Ref. 38). These studies suggest that amyloid fibril formation by some TTR mutants might be triggered by tetramer dissociation to a compact non-native monomer with low conformational stability, which results in partially unfolded monomeric species with a high tendency for ordered aggregation into amyloid fibrils (Ref. 38). In senile systemic amyloidosis where normal non-mutated TTR is deposited in the heart, it has been hypothesised that amyloid formation is related to proteolytic events, as isolated fibrils in this situation are mainly composed of TTR fragments (Ref. 16).

The precise trigger for TTR aggregation as amyloid is unknown and constitutes a major activity in TTR amyloidosis research. Similarly, an additional focus in TTR studies has been the analysis of where aggregation occurs (see next section).

Where does TTR aggregation take place?

Electron microscopy performed in nerve specimens in the early days of FAP research described 'bundles of amyloid fibrils that appeared contiguous with collagen and Schwann cells or fused with the Schwann cell basement membrane although did not penetrate beyond' (Ref. 39). Thus, the interstitial milieu is likely to be the site of TTR aggregation. In fact, upon diluting TTR in vitro to concentrations compatible with the interstitial milieu, tetrameric TTR dissociates into monomeric species, which then aggregate as described above (Ref. 38).

A monoclonal antibody, mab 39-44, reacting with high-molecular-weight aggregates of TTR, but not with tetrameric TTR, was recently generated and characterised (Ref. 40). This antibody recognises a cryptic epitope that is expressed in some isolated recombinant amyloidogenic mutants and in ex vivo amyloid; furthermore, it specifically recognises, in a direct enzyme-linked immunoassay (ELISA), plasma TTR from carriers of different mutations associated with FAP, both in asymptomatic individuals and patients. By contrast, it does not react with plasma TTR from healthy individuals, or carriers of non-pathogenic mutations (Ref. 41). Since neither monomeric species nor aggregates circulate in plasma of FAP patients, mab 39-44 might recognise circulating modified tetrameric TTR in plasma of carriers of amyloidogenic mutations, which subsequently dissociates and aggregates in the tissues.

What modulates phenotypic expression?

Susbtantial differences in clinical presentation and severity of symptoms among Portuguese Val30Met kindreds are rare; only a few cases have been reported in which a more benign clinical course is observed (Ref. 15). DNA analyses of the individuals showing reduced symptoms have indicated the presence, in a different allele, of a second mutation in the TTR gene in exon 4, resulting in a Thr119Met variant.

TTR Thr119Met is an apparently non-pathogenic mutation that has been found with high frequency in the Portuguese population in the same area where FAP prevails; its presence in compound heterozygotes ameliorates the pathogenic mutation, reducing symptoms. It will be important in the future to analyse in more detail the clinical outcome of the compound heterozygotes carrying pathogenic and non-pathogenic mutations. To date, the self-assembly properties of TTR Thr119Met have been investigated. Comparative studies of the amyloidogenic TTR Val30Met and the non-

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amyloidogenic TTR Thr119Met by semi-denaturing isoelectric focusing revealed that: (1) TTR Val30Met has a higher tendency for dissociation of the tetramer into monomers than the wild-type TTR; (2) Thr119Met, by contrast, shows higher resistance to dissociation into monomers than the wild-type protein; and (3) TTR from compound heterozygotes Val30Met and Thr119Met behaves like wild-type TTR (Ref. 42). Thus, one possible way by which Thr119Met can exert anti-amyloidogenic effects is by counteracting the weaker subunit interactions of Val30Met tetramers.

Other TTR Val30Met heterozygotes have a variable clinical onset, which can be early in the third decade or late in the seventh decade. Curiously, anticipation of age of clinical onset has been observed in successive generations of some families (Ref. 43). A future search for genetic polymorphisms that might be associated with the late-onset forms of FAP seems appropriate because it is possible that a closely linked mutation might be found in such subjects, accounting for the variable clinical expression.

Modulators responsible for phenotypic diversity can be addressed by TTR transgenic mice, which have been available since 1986 (Ref. 44). More-recent studies on a transgenic strain carrying the human full-length TTR Val30Met gene, and lacking the endogeneous murine TTR, showed that serum levels of the human mutant did not correlate with amyloid deposition. Deposition in this strain occurred at 12 months in three out of six animals investigated (Ref. 45). This incomplete penetrance seems to depend on the environment: mice reared under specific-pathogen-free conditions do not develop amyloid, suggesting that inflammatory stimuli might be part of the cascade of events leading to amyloidogenesis.

How does aggregation contribute to cell death?

Cellular toxicity and neurodegeneration in FAP are poorly understood. Increased expression of the receptor for glycation end products (RAGE) has been observed in TTR-amyloid-laden tissues, and binding of RAGE by fibrillar TTR triggers activation of the transcription factor NF-κB (Ref. 46). RAGE is a member of the immunoglobulin superfamily with a broad repertoire of ligands in addition to amyloid-associated macromolecules, including products of non-enzymatic glycoxidation [advanced glycation end-products (AGEs)], pro-inflammatory mediators (S100/calgranulins) and amphoterin (Ref. 47). In each case, the receptor recruits signal-transduction mechanisms, often resulting in a sustained and pathogenic inflammatory and stress response. This response might underlie peripheral nerve dysfunction; analyses of nerve biopsy samples from Portuguese FAP patients at different stages of the disease, compared with age-matched controls, by semiquantitative immunohistology and in situ hybridisation, demonstrated upregulation in axons of pro-inflammatory cytokines (tumour necrosis factor and interleukin 1) and the inducible form of nitric oxide synthase, as well as increased tyrosine nitration and activated caspase-3 (Ref. 48). These are all indications of pathogenic inflammation and stress in degenerating nerve fibres. Further dissection of neuronal perturbation in FAP, particularly before overt amyloid deposition, will further elucidate neurodegeneration in FAP and might suggest other avenues for treatment.

Clinical implications/applications

At the present time, the only treatment for FAP of proven efficacy is orthotopic liver transplantation. This approach was shown to virtually eliminate variant TTR from the plasma of patients with FAP (Ref. 49), and serial serum amyloid P component scintigraphy subsequently demonstrated regression of amyloid in large solid organs such as spleen in which TTR amyloid deposits could be imaged (Ref. 50). Clinically, improvement has been reported in autonomic function, such as gastrointestinal symptoms, following liver transplantation (Ref. 50). Many centres worldwide now routinely perform liver transplantation for FAP, and the procedure has been developed to include split liver transplants, partial related donor transplants, and domino transplants in which the explanted FAP liver is re-utilised in patients with life-threatening liver diseases (Refs 51, 52). Early reports from a world registry based in Sweden indicated a transplant-related mortality rate of ~20%, although this has lately been reduced by experience and earlier timing of surgery. Ideally, surgery should be performed in the first year of clinical disease (Ref. 53). However, liver transplantation does not provide a practical means of treating a large number of patients and other forms of therapy are being pursued.

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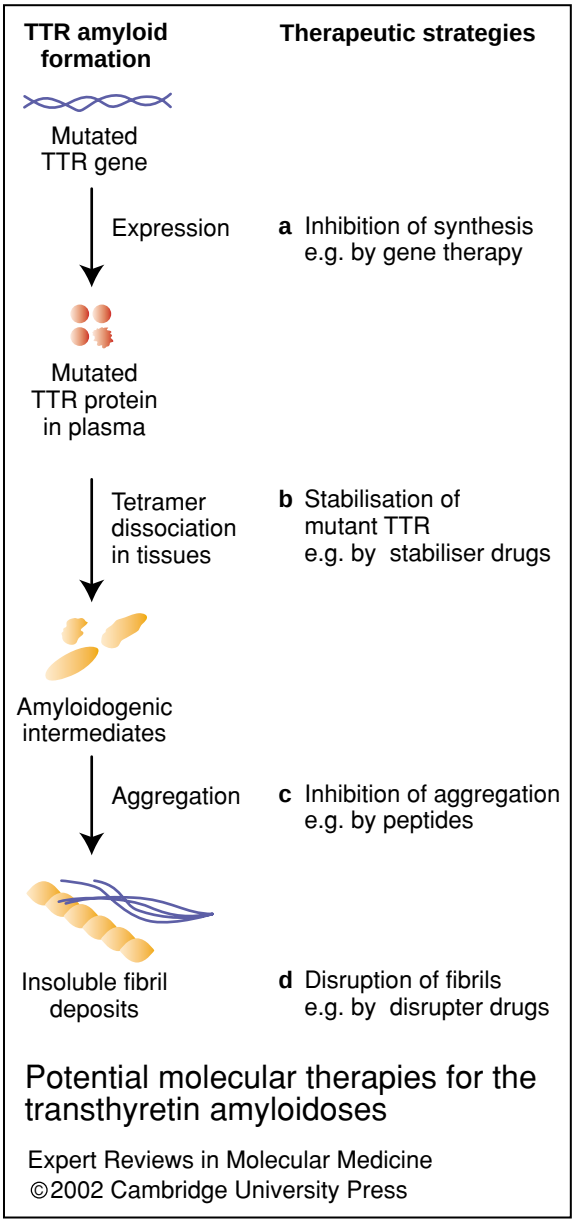

Figure 4. Potential molecular therapies for the transthyretin amyloidoses. Procedures that might block the amyloidogenic property of TTR include (a) inhibition of synthesis of mutated TTR, (b) stabilisation of the soluble circulating amyloid precursor, (c) inhibition of aggregation of amyloidogenic intermediates and (d) disruption of insoluble deposits **(fig004msp)**.

Procedures that specifically block the synthesis of mutant TTR (e.g. gene therapy) might prove effective in treating TTR amyloidoses. Other potential alternatives include stabilisation of the native conformation of TTR, with the aim of providing protective effects similar to those observed with the non-pathogenic Thr119Met mutation described above. Efforts have been made to design drugs able to bind TTR in the central hydrophobic channel that runs through the molecule, at the position where the hydrophobic hormone thyroxine binds, to prevent dissociation into monomers (Fig. 4). X-ray crystallographic analyses of different TTR–stabiliser complexes have elucidated the binding modes in the hormone-binding cavity and contacts between adjacent TTR subunits (Ref. 54). So far, these drugs have been shown to act in vitro and studies in vivo are eagerly awaited. Furthermore, sulphite has been shown both in vitro and in vivo to prevent TTR tetramers from dissociating, but the structural basis for this effect has not been elucidated (Ref. 55).

Another class of drugs with potential use in TTR amyloidosis are fibril disrupters (Fig. 4). Recently, 4'-deoxy-4'-iododoxorubicin (IDOX) has proved useful in vitro as a tool for disrupting TTR amyloid fibrils into amorphous material, as assessed by electron microscopy (Ref. 56), but it is cardiotoxic. In order to develop a non-toxic analogue of IDOX, the molecular interactions between IDOX and Leu55Pro TTR (which is in an 'amyloid-like' oligomer state) have been modelled (Ref. 57), allowing the design of other agents with fibril-disrupting properties. It should be noted that drugs that disrupt TTR amyloid might also be efficacious in other types of amyloidosis – for example in Alzheimer's disease and the prion disorders.

Finally, when more is known about the mechanisms associated with cell death in TTR-amyloid-laden tissues, inhibitors that block specific transduction cascades might be applied to counteract inflammatory and apoptotic effects.

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Further reading, resources and contacts

The Familial Amyloidotic Polyneuropathy World Transplant Register, aimed at clinicians, promotes and monitors frequency and mortality rates of liver transplantations for familial amyloidotic polyneuropathy.

http://www.fapwtr.org/

Website providing discussion, news and comments on familial amyloidotic polyneuropathy, aimed at patients:

http://www.webnote.net/home/paf/index.html

Website of the journal *Amyloid* (The Journal of Protein Folding Disorders) where articles on transthyretin amyloidoses are regularly published:

http://www.parthpub.com/amyl/home.html -

Website listing transthyretin mutations:

http://www.ibmc.up.pt/~mjsaraiv/ttrmut.html

OMIM (Online Mendelian Inheritance in Man) entry for transthyretin:

http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?176300

Clinical profile of transthyretin amyloidoses at GeneTests·Gene Clinics website:

http://www.geneclinics.org/servlet/access

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Features asssociated with this article

Figures

Figure 1. Features of amyloid fibrils (fig001msp).
Figure 2. Synthesis, circulation and uptake of transthyretin (fig002msp).
Figure 3. The transthyretin dimer (fig003msp).
Figure 4. Potential molecular therapies for the transthyretin amyloidoses (fig004msp).

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