Received: 24 January 2025 | Accepted: 25 March 2025

DOI: 10.1111/bjh.20070

REVIEW

The molecular landscape of AL amyloidosis

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Funding information
The Israeli Ministry of Innovation, Science and Technology, Grant/Award Number: 0005792

Summary
Amyloid light-chain (AL) amyloidosis is a systemic clonal plasma cell disorder characterized by the production and deposition of misfolded immunoglobulin light chains (LCs), resulting in multiorgan dysfunction. Due to its intricate molecular mechanisms and diverse organ involvement, the disease poses significant diagnostic and therapeutic challenges. This review explores the molecular landscape of AL amyloidosis, emphasizing genetic, transcriptomic and proteomic alterations. Key findings include chromosomal abnormalities, somatic mutations, aberrant gene expression, disrupted protein folding pathways and the role of cytokine and chemokine secretion. These factors collectively drive the overproduction and destabilization of amyloidogenic LCs, leading to organ-specific amyloid deposition, clinical heterogeneity and variable patient outcomes. Despite therapeutic advancements, the disease's complexity challenges the development of effective biological models. Progressing towards personalized therapies requires the development of preclinical models and the identification of biomarkers and molecular data to design targeted interventions. This review highlights the importance of integrating DNA, RNA and protein-level analyses to deepen the understanding of AL amyloidosis pathogenesis. Such insights are pivotal for improving diagnostics, prognostics and therapeutic strategies, ultimately advancing precision medicine for this challenging disease.

KEYWORDS
AL amyloidosis, immunoglobulin light chains, molecular mechanisms

INTRODUCTION

The amyloidoses are a group of diseases characterized by the formation of extracellular protein aggregates known as amyloid, which are rich in β-sheet structures and result from protein misfolding. Over 40 distinct precursor proteins have been implicated in various forms of amyloidosis.[1] Amyloid light-chain (AL) amyloidosis, one of the most prevalent forms of systemic amyloidosis, has an incidence of 3–12.7 cases per million patient years.[2] It is a clonal plasma cell (or less often B-cell) disorder, leading to overproduction of immunoglobulin light chains (LCs) with amyloidogenic properties.[3] In normal physiology, immunoglobulins are secreted as disulphide-bonded complexes consisting of two heavy chains and two LCs.[4] The LCs of immunoglobulins are composed of an N-terminal variable domain (VL) and a constant domain (CL). The VL domain sequence is generated through DNA rearrangements involving variable (V), diversity (D) and joining (J) gene segments, which collectively contribute to the diversity of the antibody repertoire, essential for an effective immune response.[5] This rearrangement process is mediated by the recombination-activating genes *RAG1* and *RAG2*, which introduce double-strand breaks at specific regions of the DNA. After cleavage, the repair and joining of these DNA ends form coding joints that encode the antigen-binding sites of immunoglobulins.[6] Furthermore, during the later stages of B-cell differentiation, the V region exon

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undergoes targeted somatic hypermutation, further enhancing VL domain diversity.[5] In AL amyloidosis, each patient exhibits unique somatic mutations and a specific LC amino acid sequence, resulting in a distinct monoclonal LC sequence that forms amyloid deposits, evades cellular quality control and causes multiorgan dysfunction.[7] These amyloid precursor LCs can subsequently be internalized by immune cells or deposited extracellularly in multiple organs as amyloid.[8]

The clinical presentation of AL amyloidosis varies based on organ involvement and fibril deposition,[9] with 69% of patients showing multiorgan involvement.[10] Prognosis is influenced by the degree of organ involvement (especially heart), treatment response and coexisting diseases such as multiple myeloma (MM).[11]

Over the past decades, progress has been made in elucidating the molecular and genetic pathogenesis of AL amyloidosis, encompassing various aspects at the DNA, RNA and protein levels. This review summarizes the molecular mechanisms underlying AL amyloidosis, addresses challenges in disease modelling and identifies unmet needs for future translational research.

DNA-LEVEL ALTERATIONS

Genomic instability is common in AL amyloidosis, with ~80% of patients displaying at least one chromosomal abnormality using the fluorescence in situ hybridization (FISH) technique. Of those, 50%–70% have immunoglobulin heavy chain (*IGH*) translocations, a higher proportion than in other plasma cell disorders, which may explain the predilection of AL plasma cells to secrete excessive amounts of free light chains (FLCs).[12] Likewise, approximately half of AL amyloidosis patients secrete LCs only,[13] without intact immunoglobulin secretion, a proportion that is approximately threefold higher than what is seen in MM.[14] Chromosomal aberrations impact various pathogenic pathways, prognosis and clinical decisions.[15–17] The following section will focus on genetic aberrations at the DNA level and their clinical implications.

Normal chromosome profile

Approximately 20% of individuals with AL amyloidosis do not exhibit chromosomal aberrations when studied by interphase FISH. This subgroup typically has a lower plasma cell burden, less cardiac involvement and longer progression-free survival (PFS) and overall survival (OS) rates than patients with chromosomal aberrations,[18] suggesting that the absence of chromosomal abnormalities could be a favourable prognostic indicator. However, FISH data in these patients may be unreliable, with a lower plasma cell burden impeding enrichment of the clonal plasma cell complement for appropriate FISH testing.

Translocations involving the *IGH*

IGH translocations are the most prevalent cytogenetic abnormality in AL amyloidosis. These translocations involve different chromosomes aligning with the *IGH* locus on chromosome 14. These translocations contribute to LC-only secretion and dysregulation of genes, as summarized in Table 1 and Figure 1.

t(11;14)

The t(11;14) translocation, which juxtaposes the *IGH* locus on chromosome 14 with the cyclin D1 (*CCND1*) oncogene on chromosome 11, is the most common cytogenetic abnormality in AL amyloidosis, seen in 40%–60% of patients.[15,19] Its prognostic significance is treatment dependent. Patients with t(11;14) treated with bortezomib-based regimens tend to have inferior haematological response rates, higher relapse rates and worse OS compared to non-t(11;14) patients.[16] However, those treated with melphalan and dexamethasone or high-dose melphalan followed by autologous stem cell transplantation (ASCT) have similar outcomes to those without t(11;14).[15,16]

Daratumumab, a CD38 monoclonal antibody, has shown strong efficacy in AL amyloidosis, both in the relapsed/refractory setting as well as in the frontline setting in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd). Importantly, D-VCd overcomes the poorer outcomes associated with t(11;14) patients treated with bortezomib.[20,21]

The phase III Andromeda trial demonstrated that treatment with D-VCd resulted in significantly higher haematological complete response (CR) (53%) and ≥VGPR rates (78%) compared to VCd (18% and 49%, respectively) in previously untreated patients. Organ responses were also significantly improved.[22] These outstanding response rates have led to D-VCd being the currently accepted frontline therapy for AL amyloidosis. A subsequent analysis of the Andromeda trial by baseline FISH reported that the haematological CR rate was higher with D-VCd compared to VCd among patients harbouring t(11;14). This was confirmed in a real-world study by Chakraborty et al.[17] who reported that D-VCd was effective in achieving deeper haematological responses than VCd in patients with t(11;14).

Biologically, t(11;14) is associated with increased B-cell leukaemia/lymphoma 2 (*Bcl-2*) expression and elevated *Bcl-2/MCL-1* and *Bcl-2/BCL2L1* ratios.[23] This may be related to the ability of these cells to sustain and survive the increased proteotoxic stress associated with the production of amyloidogenic LCs or other factors, such as proteasome inhibition.[24] Venetoclax, a Bcl-2 inhibitor, has shown promise in the relapsed/refractory setting for t(11;14) patients, effectively targeting this biological vulnerability.[25,26]

TABLE 1 Chromosomal aberrations in AL amyloidosis.

Aberration	Frequency	Associated genes	Clinical impact	Prognosis and treatment
t(11;14)	40%–60%	CCND1 Bcl-2	Related to the anti-apoptotic process and cell cycle regulation	Lower haematological response and OS in bortezomib-treated patients. No discriminatory effect among melphalan-, daratumumab- and ASCT-treated patients
t(4;14)	2%	FGFR3, MMSET	Associated with plasma cell proliferation	Bortezomib-based regimens effective in MM. No data regarding AL
t(14;16)	2%–4%	MAF	Linked to regulating cell growth and differentiation	Limited data on prognosis
t(14;20)	1%	MAFB	Upregulation of CCND2 and NOTCH2, plasma cell proliferation	Considered high-risk, associated with poor outcomes. Limited data on treatment
t(6;14)	Rare	CCND3	Increased expression of CCND3	Standard risk in MM; unclear prognostic role in AL amyloidosis
Trisomies	20%	—	Elevated dFLC, higher plasma cell burden	Associated with more malignant disease and shorter survival
Gain of 1q21	20%–30%	—	Associated with a higher plasma cell burden and concomitant MM	Inferior outcomes with melphalan/dexamethasone and for DRD Prognostic marker for patients treated with melphalan/dexamethasone
Monosomy/Deletion of 13q	30%–36%		Cardiac involvement, high dFLC levels, higher BM plasms cells	No significant survival difference with current treatments compared to patients without deletion; addition of daratumumab to CyBorD shows improved haematological responses
Deletion of 17p	3%–5%	TP53	Aggressive plasma cell clone, inferior OS	High-risk cytogenetic abnormality, poor prognosis

Abbreviations: ASCT, autologous stem cell transplantation; Bcl-2, B-cell leukaemia/lymphoma 2; BM, bone marrow; CCNCD1, cyclin D1; CCND2, cyclin D2; CCND3, cyclin D3; dFLC, differential free light chain; DRD, daratumumab, lenalidomide, dexamethasone; D-VCD: daratumumab, bortezomib, cyclophosphamide and dexamethasone; FGFR3, fibroblast growth factor receptor 3; FLC, free light chain; MM, multiple myeloma; MMSET, multiple myeloma SET domain; NOTCH2, notch receptor 2; OS, overall survival.

t(4;14)

This translocation, seen in 2% of AL amyloidosis patients,[15] dysregulates two genes with oncogenic potential: the fibroblast growth factor receptor 3 (*FGFR3*) on chromosome 14 and multiple myeloma SET domain (*MMSET*) genes on chromosome 4.[27] This translocation, associated with plasma cell proliferation and cell cycle regulation, suggesting a survival or proliferative signal.[27] No prognostic data regarding this translocation exist in AL amyloidosis.

t(14;16)

The t(14;16) translocation occurs in ~4% of AL amyloidosis patients[15] and fuses the *IGH* gene on chromosome 14 with the *MAF* gene on chromosome 16. This gene is a transcription factor that binds to the cyclin D2 (*CCND2*) promoter and has a role in regulating cell growth and differentiation.[28] Due to being an uncommon cytogenetic aberration, limited data exist on treatment outcomes, preventing definitive conclusions.

Other *IGH* translocations

Rare *IGH* translocations in AL amyloidosis include t(14;20) (1%), which upregulates the *MAFB* transcription factor,[15,18,29] and t(6;14), which elevates *CCND3* expression.[30] *MAFB* overexpression upregulates *CCND1*, *CCND2* and *NOTCH2*, indicating shared mechanisms in both *MAF* and *MAFB* dysregulated plasma cell malignancies.[31] While t(14;20) and t(6;14) have defined prognostic roles in MM,[28] their impact on AL remains unclear.

Other chromosomal aberrations

Trisomies

Trisomies (also referred to as hyperdiploidy) occur in 20%–30% of AL amyloidosis patients[18,32] and involve chromosomes 3, 4, 5, 7, 9, 11, 15, 17, 18 and 19.[18,32–34] These abnormalities negatively impact survival[15,18,35] and are associated with elevated differential free light chain levels (dFLC, i.e. the difference between the involved to uninvolved FLCs, a measure of disease burden in AL) and bone marrow (BM) plasma cells.[18]

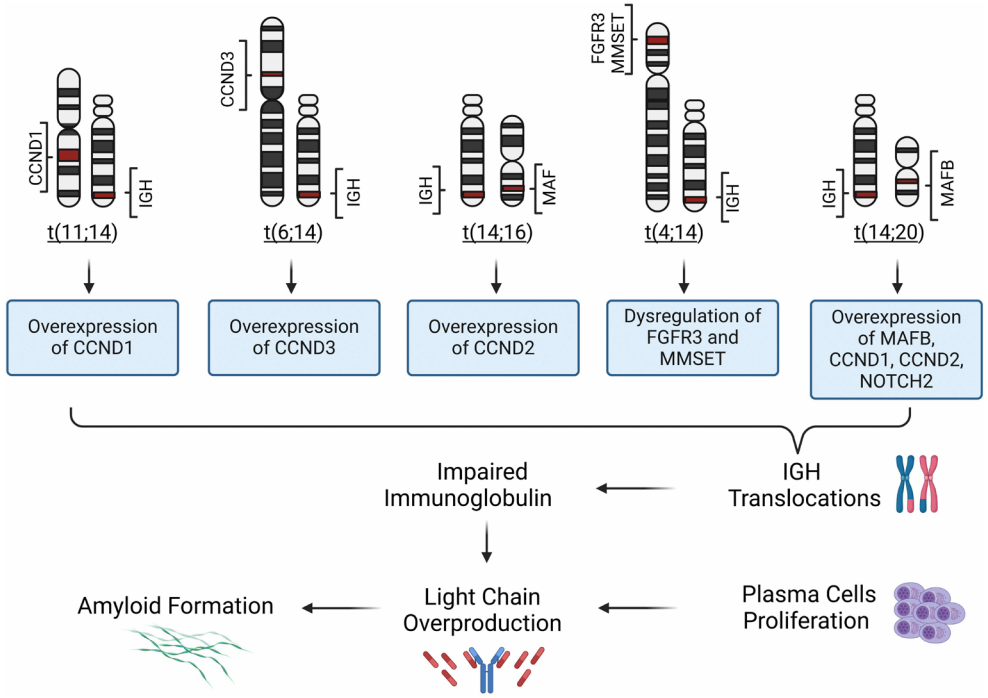

FIGURE 1 Chromosomal translocations and molecular mechanisms leading to plasma cell proliferation and light chain overproduction. Key immunoglobulin heavy chain (*IGH*) translocations associated with plasma cell dyscrasias and their downstream molecular consequences. These genetic abnormalities contribute to plasma cell proliferation, impaired immunoglobulin synthesis and excessive production of monoclonal light chains. Created in https://BioRender.com.

Trisomies 9 and 19 are the most common and correlate with worse PFS.[36] The reasons for the adverse impact of trisomies in AL amyloidosis remain unclear. One potential explanation is that trisomies are associated with a higher rate of clonal evolution, suggesting a more malignant disease potential. Additionally, patients with trisomies often exhibit higher dFLC levels and a greater plasma cell burden, which may result in increased amyloid fibril formation in target tissues and subsequent organ dysfunction.

Gain of 1q21

Approximately 20%–30% of AL amyloidosis patients exhibit gain of 1q21, similar to MM.[18,32,37] This abnormality is associated with higher plasma cell burden, concomitant MM,[12,17] lower haematological response rates and inferior survival when treated with melphalan/dexamethasone.[37] More recently, 1q21 gain was shown to be associated with a lower deep haematological response rate to daratumumab-based front-line therapy compared to patients without this aberration,[17] albeit this finding was not observed in a post-hoc analysis of the Andromeda dataset.[22] Gain of 1q21 was also associated with inferior outcomes for patients receiving daratumumab, lenalidomide and dexamethasone combination.[38] However, 1q21 gain did not confer worse outcomes among AL patients treated with high-dose melphalan followed by ASCT.[39]

Monosomy 13/deletion of 13q

Monosomy 13 or 13q deletion occurs in 30%–36% of AL amyloidosis patients[15,18] and is associated with cardiac involvement,[18,36] high dFLC levels and elevated BM plasma cells.[18,40] It does not impact survival with melphalan-based treatments or ASCT[37,39] but benefits from daratumumab addition to front-line VCd, similar to other cytogenetic groups.[17,22]

Deletion of 17p

The 17p deletion is a high-risk abnormality that occurs in 3%–5% of AL amyloidosis patients and involves the tumour suppressor gene *TP53*.[18,34,41] Since *TP53* is related to cell proliferation, this alteration promotes an aggressive plasma cell clone[42] and inferior OS.[18,41]

DNA mutations

Point mutations

Point mutations can lead to the thermodynamic instability of LCs, promoting LC misfolding and amyloid fibril formation. Their effect depends on mutation location within the LC structure.[43,44] A leucine-to-valine substitution (L81V) in the variable light (VL) domain has been

linked to amyloid fibril formation by decreasing the VL domain stability. Similarly, the replacement of arginine with asparagine at position 61 (R61N) in the kappa VL domain destabilizes this domain, affects protein misfolding and contributes to the pathogenesis of AL amyloidosis.[45] Additional point mutations implicated in AL amyloidosis include Ankyrin Repeat and SOCS Box Containing 15 [*ASB15* (c.844C>T)], Activating Signal Cointegrator 1 Complex Subunit 3 [*ASCC3* (c.1595A>G)], *HIST1H1E* (c.311C>T) and *KRAS* (c.35G>A), which are associated with inferior OS.[46] Whole exome sequencing of clonal plasma cells identified 662 mutated genes across 27 AL patients.[36] Of these, only 37 genes were recurrently mutated (i.e. mutations observed in more than one individual), including FAT atypical cadherin 4 (*FAT4*), immunoglobulin lambda like polypeptide 5 (*IGLL5*), mucin 16 (*MUC16*) and slingshot protein phosphatase 2 (*SSH2*), which were the most frequently mutated genes. Recurrent mutations commonly found in MM, such as *DIS3* and dual specificity phosphatase 2 (*DUSP2*), were rarely observed in AL amyloidosis. Mutations in *NRAS*, *BRAF* and *TRAF*, which are known to be associated with MM progression, were not yet identified in AL amyloidosis patients.[36,47] Additionally, *IGH* repertoire analysis revealed that the *IGHV3-48* gene is most frequent in AL cases with renal involvement, while *IGHV3-30* predominates in MM.[36] These findings suggest distinct genetic landscapes between AL amyloidosis and MM, with unique recurrent mutations and *IGH* usage patterns contributing to AL amyloidosis pathogenesis and clinical manifestations.

Single-nucleotide polymorphism (SNP)

SNP studies have identified genetic alterations contributing to AL amyloidosis pathogenesis. SNPs can affect various genes involved in the stability and functionality of LCs, which are crucial in the development of amyloid fibrils.

Filho et al. showed that rs4487645 (G>T), located on chromosome 7p15.3, is associated with the risk of both MM and AL.[48] This SNP is mapped within a binding site for interferon regulatory factor 4 (*IRF4*) in a strong enhancer element upstream of cell division cycle associated 7 like (*CDCA7L*) (MYC-interacting gene), suggesting a pathway involving *MYC* and *IRF4*. Other SNPs include rs79419269, located near the *SMARCD3* gene on chromosome 7q36.1; an SNP within either the Snf2-related CREBBP activator protein (*SRCAP*) or proline rich 14 (*PRR14*) gene on chromosome 16p11.2; and chromobox 7 (*CBX7*) on chromosome 22q13.1. These genetic loci suggest a functional role in AL amyloidosis, particularly through their involvement in chromatin remodelling.[48]

Immunoglobulin variable light (IGLV)

The *IGLV* gene family plays a significant role in shaping the diversity of the antibody repertoire, consisting of various gene segments encoding the variable regions of lambda LCs. These segments are classified into subfamilies based on sequence similarities. *IGLV1*, *IGLV2*, *IGLV3* and *IGVL6* are major subfamilies of the lambda LC variable region gene family, which have been implicated in AL amyloidosis due to their tendency to misfold and form amyloid fibrils, often exhibiting organ-specific involvement.[49–51] *IGLV3-21* is linked to cardiac involvement, while *IGLV1-44*, *IGLV1-51* and *IGLV6-57* are associated with cardiac and renal involvement.[34,49,52,53] *IGVL6-57* is linked to t(11;14), and *IGLV3-01* is less commonly associated with advanced heart disease or renal involvement.[49] Additionally, the *IGKV1-33* variant is associated with liver involvement and higher circulating FLCs.[54]

RNA EXPRESSION CHANGES

Aberrant RNA expression in AL amyloidosis can impact plasma cell generation, LC misfolding, and regulation of cell growth and apoptosis. Gene expression profiling has identified differences in gene expression between AL amyloidosis, healthy donors and MM, as shown in Figure 2 and Table 2. Several key genes contribute significantly to AL amyloidosis pathogenesis.

Cyclin D1

CCND1 is a proto-oncogene with a key role in regulating the cell cycle, particularly in the transition from the G1 to S phase.[55–59] It forms complexes with cyclin-dependent kinase (Cdk) 4 and Cdk6, which are necessary for cell cycle progression and for inactivating retinoblastoma protein (pRB), thereby promoting gene activity and facilitating cell cycle transition.[60] Overexpression of *CCND1* in AL amyloidosis is associated with higher levels of endoplasmic reticulum (ER) protein processing genes, essential for protein synthesis and folding, such as SEL1L adaptor subunit of SYVN1 ubiquitin ligase (*SEL1L*), Sec63 and protein disulphide isomerase family A member 6 (*PDIA6*). AL amyloidosis patients with *CCND1* overexpression produce more FLCs and fewer intact M-proteins. In multivariate analysis, *CCND1* expression was an independent predictor of survival in AL.[61] Finally, *CCND1* is frequently mutated in various cancers, with overexpression observed in AL amyloidosis both with and without translocation t(11;14).[61–63]

BCL2, anti-apoptotic family members

BCL2 family members, including BCL2, MCL1 and BCL2L1, are anti-apoptotic proteins involved in immune response and apoptosis regulation.[64] Dysregulation of these genes contributes to haematological malignancies reliant on anti-apoptotic signalling.[65,66] Genomic profiling of BM-derived plasma cells from AL amyloidosis and MM

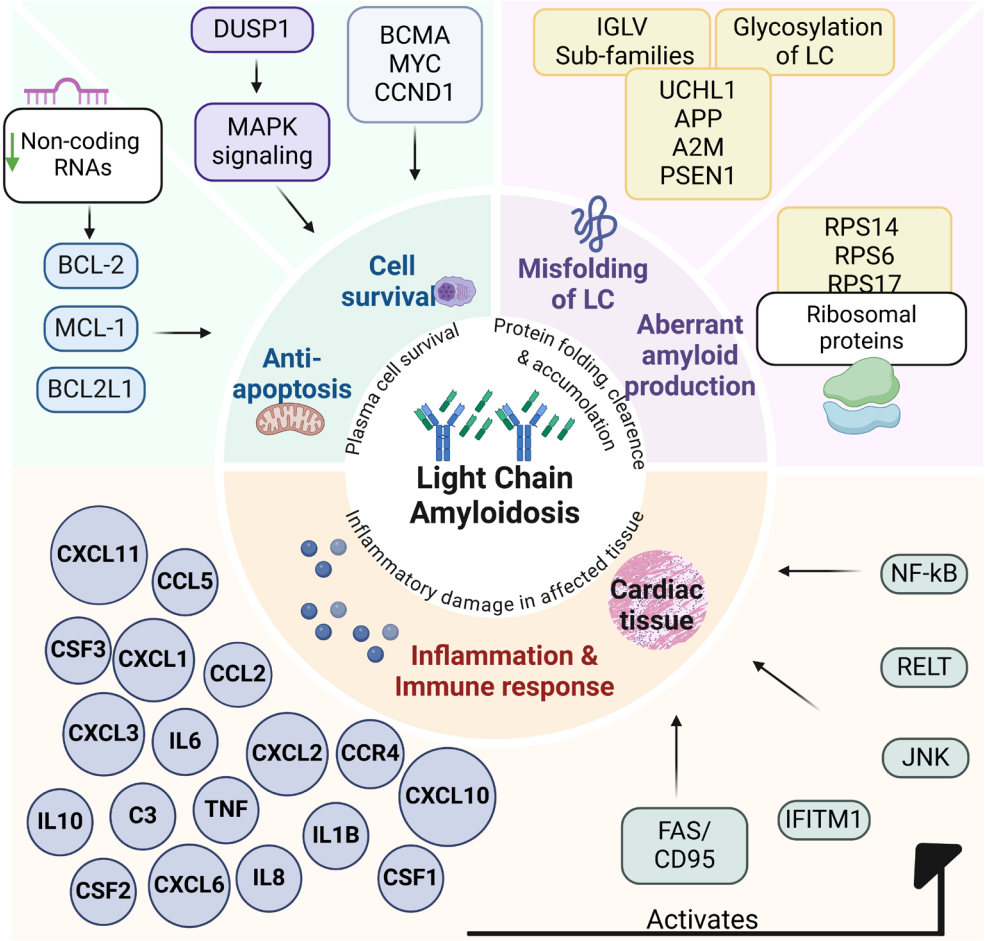

FIGURE 2 Molecular and cellular mechanisms contributing to AL amyloidosis. This schematic highlights the complex interplay of pathways involved in the pathogenesis of AL amyloidosis. Key processes include plasma cell survival, protein folding, clearance and accumulation, as well as inflammatory involvement (mediated by cytokines and chemokines), which contribute to organ tissue damage. Created in https://BioRender.com. AL, amyloid light-chain; LC, light chain.

patients identified abnormal expression of these genes, indicating dependence on *MCL1* and *BCL2* for cell survival.[23,26,67] Overexpression of BCL2 may promote plasma cell survival and LC production associated with mitochondrial dysfunction and oxidative phosphorylation.[23] MicroRNAs (miRNAs) such as miR-9-5p and miR-181a-5p can impact AL progression by regulating the BCL2 family members.[23]

Venetoclax, a BCL2 inhibitor, showed promising results in MM patients with t(11;14) and high BCL2 expression.[68] Studies have also found a correlation between translocation t(11;14) and high *BCL2/BCL2L1* ratios in AL amyloidosis, with venetoclax effectively inducing haematological remissions in relapsed/refractory AL amyloidosis patients with t(11;14).[25,26]

DUSP1 and MAPK

Dual specificity phosphatase 1 (*DUSP1*), a negative regulator of the mitogen-activated protein kinase (MAPK) signalling pathway,[69] is downregulated in AL amyloidosis, leading to MAPK pathway activation. This pathway is essential for regulating various cellular processes, including proliferation, differentiation and apoptosis; however, in haematological malignancies, its activation drives uncontrolled cell growth, survival and tumour progression.[70–72] Dysregulation of MAPK-related genes and miRNAs has been observed in AL amyloidosis, highlighting the pathway as a significant therapeutic target that may lead to more tailored and effective treatments for AL amyloidosis patients.[73]

Other genes

Several genes are overexpressed or underexpressed in AL amyloidosis, though their exact biological roles and prognostic significance remain unclear.[63,67,74,75] For example, NADH:oxidoreductase subunit S6 (*NDUFS6*), TMEM66, coiled-coil domain containing 71 (*CCDC71*) and eukaryotic translation initiation factor 3 subunit L (*EIF3L*) are all upregulated in AL amyloidosis.[74] *EIF3L* is involved in protein synthesis, supporting increased ribosome production characteristic of cancer cells.[76,77] Other deregulated genes in AL

TABLE 2 RNA expression changes in AL amyloidosis.

Gene	Up- or downregulated	Role in disease	Impact on pathogenesis	Prognosis and treatment
IGLV subfamilies	Upregulated	Misfolding of light chains	IGLV3-21 is linked to cardiac involvement, while IGLV1-44, IGLV1-51 and IGLV6-57 are linked to both cardiac and renal involvement	Overrepresentation of certain IGLV genes linked to specific organ involvement
BCL2 family	Upregulated	Anti-apoptotic signalling and immune response modulation	Overexpression linked to plasma cell proliferation, producing abnormal LCs associated with mitochondrial signalling pathways (e.g. oxidative phosphorylation, sirtuin signalling and mitochondrial dysfunction)	BCL-2 inhibitor (venetoclax) is effective in t(11;14) patients
DUSP1	Downregulated	Negative regulator of MAPK pathway	MAPK activation leads to uncontrolled cell growth	Potential therapeutic target for tailored treatments with MAPK inhibitors
RPS14 RPS6 RPS17	Downregulated	Essential for ribosome function and protein synthesis	May lead to aberrant amyloid protein production	Potential therapeutic in AL has not been established
IFITM1	Upregulated	Immune response	Its involvement in the specific mechanisms of AL amyloidosis pathogenesis has not been established	A prognostic factor for poor survival in solid tumours, but there is no clear evidence regarding AL
UCHL1	Upregulated	Clearing and regulating misfolded proteins	May be involved in regulating protein degradation through deubiquitination and maintaining homeostasis	Potential therapeutic in AL has not been established
APP A2M	Upregulated	Involved in protein processing and clearance and protein folding	May be involved in protein misfolding, clearance and inflammation	May exacerbate the accumulation of amyloid fibrils, influencing the severity and progression of the disease Targeting these proteins may present opportunities for therapeutic intervention
PSEN1	Downregulated	Regulate protein processing and folding	Associated to dysregulation of common pathways related to protein clearance, degradation and folding in AL amyloidosis	Potential therapeutic in AL has not been established
CASP3	Downregulated	Involved in proteolysis and peptidolysis	Deregulation may play a significant role in abnormal protein processing and folding in AL amyloidosis	Potential therapeutic in AL has not been established
MYC	Upregulated	A transcription factor that regulates genes involved in cell growth, metabolism and proliferation	Upregulation of MYC can drive plasma cell proliferation, contributing to the clonal expansion of LC-producing plasma cells. This leads to increased production of misfolded light chains, forming amyloid deposits	MYC upregulation is often associated with more aggressive disease phenotypes and poorer prognosis. Targeting MYC or MYC-regulated pathways might be a potential therapeutic approach, although direct MYC inhibitors are not yet widely available

Abbreviations: A2M, alpha-2-macroglobulin; APP, amyloid beta precursor protein; BCL-2, B-cell lymphoma 2; CASP3, caspase 3; CCNCD1, cyclin D1; DUSP1, dual specificity phosphatase 1; FLC, free light chain; IFITM1, interferon-induced transmembrane protein 1; IGLV, immunoglobulin variable light; LC, light chain; MAPK, mitogen-activated protein kinase; PSEN1, presenilin 1; RPS14, ribosomal protein S14; RPS17, ribosomal protein S17; RPS6, ribosomal protein S6; UCHL1, ubiquitin C-terminal hydrolase L1.

amyloidosis include amyloid beta precursor protein (*APP*), alpha-2-macroglobulin (*A2M*), presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), ubiquitin C-terminal hydrolase L1 (*UCHL1*) and caspase 3 (*CASP3*).[63]

A transcriptomic profiling of AL amyloidosis has shown a gene expression signature similar to that of normal plasma cells, but with the deregulation of several genes. The tumour suppressors cadherin gene (*CDH1*) and regulator of calcineurin (*RCAN*), and proapoptotic genes glioma pathogenesis-related protein 1 (*GLIPR1*) and Fas cell surface death receptor (*FAS*) were all downregulated in AL. In contrast, interferon-induced transmembrane protein 1 (*IFITM1*), which has been associated with more aggressive solid tumours, was upregulated.[75] Additionally, Alameda et al. found that over half of the genes downregulated in AL amyloidosis are linked to oxidative phosphorylation, MYC or ribosome biogenesis, indicating ribosome dysfunction in AL amyloidosis.[67,74] Overall, a detailed exploration of RNA expression changes and gene dysregulation provides insights into the molecular mechanisms underlying AL amyloidosis and identifies potential therapeutic targets that warrant further investigation.

PROTEIN MODIFICATIONS, MISFOLDING AND AGGREGATION

Aberrant protein expression was also shown to contribute to AL amyloidosis pathogenesis (Table 3). In AL amyloidosis, the excessive secretion of immunoglobulin LCs with or without intact immunoglobulin suggests defects in the ER's quality control mechanisms, which include the unfolded protein response (UPR) and various chaperone proteins. These mechanisms are crucial for maintaining protein homeostasis, particularly in the context of misfolded proteins. Bianchi et al. highlighted that dysregulation of this protein homeostasis network plays a central role in AL amyloidosis and suggested that targeting the UPR could be a promising therapeutic strategy to enhance proper protein folding and reduce amyloid accumulation.[78] Supporting this, Rius et al. demonstrated that activation of specific UPR pathways, such as the ATF6 arm, can reduce the secretion of amyloidogenic FLCs, highlighting the potential of modulating UPR to influence disease progression.[24,79]

Beyond disruptions in protein folding, post-translational modifications (PTMs) of amyloidogenic LCs, such as disulphide bonds,[80–82] N-terminal pyroglutamate (Pyro-Glu) modifications[83,84] and glycosylation,[85–87] contribute to the pathogenesis of AL amyloidosis. These chemical modifications alter the structural stability of LCs, promoting misfolding and amyloid fibril formation. Among these, glycosylation emerged as particularly influential, affecting the solubility and aggregation propensity of LCs. Studies have demonstrated that glycosylated LCs are associated with a higher risk of disease progression, morbidity and mortality in AL amyloidosis and are a risk factor for developing AL amyloidosis among patients with monoclonal gammopathies. Glycosylation can occur through N-linked or O-linked bonds, with modifications in the variable domain of LCs potentially altering the protein folding pathway and affecting interactions with chaperone proteins, thus increasing the likelihood of misfolding and aggregation.[88] This modification also influences the interaction between amyloid fibrils and extracellular matrix components or cellular receptors, which may affect tissue distribution and toxicity of amyloid deposits.

Recent discoveries have further linked somatic mutations to glycosylation patterns in kappa-LCs, introducing new glycosylation sites strongly correlated with AL amyloidosis. For instance, the acquisition of an N-linked glycosylation site due to a mutation at position 20 of the kappa-LC primary structure creates a new sequence that allows glycosylation, which has been implicated in disease development.[89] Prado et al. observed that glycosylated LCs tend to accumulate predominantly in the liver.[90]

In addition to the role of UPR dysfunction and PTMs, matrix metalloproteinases (MMPs) have been implicated in the pathophysiology of AL amyloidosis. These proteolytic enzymes are primarily involved in the remodelling of the extracellular matrix (ECM). In AL amyloidosis, MMP-9 has been identified as being overexpressed, contributing to tissue remodelling in areas where amyloid deposits are present.[91] MMP activity can influence the breakdown of ECM, potentially facilitating the deposition of amyloid fibrils and exacerbating organ damage. On the other hand, MMPs may also degrade fibrillar deposits, promoting amyloid clearance under certain conditions. In addition to MMPs, proteolytic enzymes such as cathepsin B, K and L have been shown to degrade AL amyloid deposits, suggesting that proteolysis may regulate amyloidogenesis and fibril stability.[92] Given that amyloid fibrils are polymeric structures resulting from misfolded proteins, understanding the role of proteolytic enzymes in this context could open new avenues for therapeutic intervention. Thus, MMPs and other proteolytic enzymes may act as regulators of fibril formation or degradation, but their dysregulation can also contribute to further tissue damage, particularly in the heart and kidneys. Therefore, while these enzymes could serve as both regulators of amyloidogenesis and potential therapeutic targets, their dual role suggests that interventions targeting MMP or cathepsin activity should be approached with caution to avoid unintended tissue damage.

Cytokines and chemokines

Cytokines and chemokines are signalling molecules that mediate inflammation and immune responses, which may be critical in the deposition and clearance of amyloid fibrils. The cytokine and chemokine profile in AL amyloidosis may influence the organ involvement pattern. For instance, cardiac involvement in AL amyloidosis may be associated with unique cytokine profiles indicative of inflammation. Marin-Argany et al. showed that fibrillar aggregates of LCs can be cytotoxic

TABLE 3 Protein expression changes in AL Amyloidosis.

Protein/pathway	Role in disease	Impact on pathogenesis	Prognosis and treatment
Defects in ER quality control mechanisms (including UPR and chaperone proteins)	ER quality control dysfunction leads to extracellular aggregation of misfolded LCs, contributing to amyloid deposition in tissues	Misfolding leads to amyloid fibril formation UPR pathway dysregulation (especially ATF6 and XBP1) results in defective protein homeostasis	Targeting UPR pathways could enhance proper protein folding and reduce amyloid accumulation. AFT6 and XBP1 activation improves ER retention of misfolded LCs by enhancing interactions with chaperones with potential therapeutic value
PTMs of amyloidogenic LCs	Disulphide bonds, N-terminal pyroglutamate modifications and glycosylation alter LC structure and promote misfolding and aggregation	These modifications destabilize LCs, increasing misfolding and amyloid fibril formation. Glycosylation is especially associated with increased risk of disease progression, morbidity and mortality. Glycosylated LCs have a propensity to accumulate in specific organs (e.g. liver)	Glycosylated LCs are linked with poor outcomes. New therapeutic interventions targeting glycosylation sites may reduce organ-specific amyloid deposits
MMPs and proteolytic enzymes (cathepsin B, K and L)	Involved in ECM remodelling and degradation of amyloid fibrils	MMP-9 overexpression contributes to tissue remodelling and may facilitate amyloid deposition in the ECM, exacerbating organ damage Conversely, MMPs and cathepsin B, K and L degrade amyloid fibrils, regulating amyloidogenesis and fibril stability	Potential therapeutic interventions targeting MMPs or cathepsins must balance promoting amyloid degradation with the risk of excessive ECM breakdown, which could worsen tissue damage
Cytokines and chemokines	Mediate inflammation and immune responses, contributing to amyloid clearance	Inflammatory cytokines, including CXCL2, IL1B, IL6 and C3, are linked to organ-specific damage, particularly in cardiac AL amyloidosis. C3 upregulation in cardiomyocytes suggests that complement may play a role in triggering inflammatory damage due to amyloid deposition	Targeting cytokine-mediated inflammation may reduce organ damage, especially in cases of cardiac involvement Immunomodulatory therapies aimed at cytokines and chemokines are potential strategies
TNF family	Regulates immune response, inflammation and apoptosis	Dual function, can promote cancer cell growth or act as tumour suppressors by inducing cell death	Dysregulation can lead to disease progression; therapies targeting TNF pathways may influence treatment
CD27 (TNFRSF7)	Expressed in mature B lymphocytes, regulates immune response and cell survival	Absence linked to MM progression, crucial for B-cell differentiation into plasma cells	Associated with poor haematological response and worse OS in AL amyloidosis patients
BCMA (TNFRSF17)	Overexpressed in plasma cells in MM and AL amyloidosis	Plays a crucial role in the regulation of B-cell development, survival and differentiation into plasma cells	Targeted by novel immunotherapy approaches in MM, currently under investigation in the management of AL amyloidosis
FAS/CD95 (TNFRSF6)	Regulates apoptosis and immune response	Dysregulation linked to aberrant immune response	Potential target for therapies related to immune modulation
RELT (TNFRSF19L)	Involved in apoptosis regulation	Dysregulation linked to aberrant immune response	Investigated for its role in disease progression and potential therapeutic interventions
The complement system	Involved in the immune response	Elevated levels of matrix-related proteins, complement proteins and enzymatic processes	Proteomic analysis of amyloid plaques in cardiac AL amyloidosis

Abbreviations: C3, complement C3; CXCL2, C-X-C motif chemokine ligand 2; ECM, extracellular matrix; ER, endoplasmic reticulum; FAS, Fas cell surface death receptor; IL1B, interleukin 1 beta; IL6, interleukin-6; LC, light chain; MM, multiple myeloma; MMPs, matrix metalloproteinases; OS, overall survival; PTMs, post-translational modifications; TNF, tumour necrosis factor; UPR, unfolded protein response.

and arrest in vitro the growth of human RFP-AC16 cardiomyocytes.[93] Adipose-derived mesenchymal stromal cells (AMSCs) can rescue the cardiomyocytes from fibril-induced growth arrest through contact-dependent mechanisms.[93] In a follow-up study, Jordan et al.[72] explored the transcriptome changes of human cardiomyocytes and AMSC in the presence of AL amyloid fibrils. This study revealed an upregulation of genes related to immune regulation and inflammatory response, such as C-X-C motif chemokine ligand 2 (*CXCL2*), interleukin 1 beta (*IL1B*), C-X-C motif chemokine ligand 3 (*CXCL3*),

interleukin-8 (*IL8*), interleukin-11 (*IL11*), interleukin-6 (*IL6*), colony stimulating factor 3 (*CSF3*), C-X-C motif chemokine ligand 1 (*CXCL1*), complement C3 (*C3*), G0/G1 switch 2 (*G0S2*) and colony-stimulating factor (*CSF*). The authors suggest that the upregulation of *C3* in cardiomyocyte cells indicates that complement may play a crucial role in the signalling cascade that induces cell damage due to amyloid deposition in cardiac AL. Additionally, *C3* may have a role in initiating an inflammatory response through the innate immunity pathway and the inflammasome. Kourelis et al.[94] conducted a proteomic analysis of amyloid plaques in cardiac AL amyloidosis. The study demonstrated that cultured cardiomyocytes exposed to AL fibrils activate the expression of complement-related genes, indicating an immune response. The analysis revealed 13 proteins that were elevated in AL plaques compared to normal cardiac tissue. These included four matrix-related proteins (COL1A1, COL1A2, COL3A1 and TIMP3), one complement protein (CFHR1), two proteins involved in enzymatic processes (GPD1 and PIK3C3) and SERPINE2.

Colony stimulating factor 2 (CSF2), CSF3, CXCL1, CXCL3, IL8 and C-X-C motif chemokine ligand 6 (CXCL6) are also pro-inflammatory cytokines that play a role in the recruitment and activation of granulocytes, macrophages and monocytes.[95–97] The upregulation of innate immune-related transcripts highlights the activation of the immune system in response to amyloid deposition. This activation may shed light on the mechanisms through which the immune system interacts with cardiomyocytes, potentially mediating either protective or detrimental effects.

A recent study that examined the transcriptome of CD138-positive cells isolated from BM samples of AL and MM patients showed that the innate immune and inflammatory response pathways are already upregulated in the clonal plasma cell population of AL. Significant differential expression was observed in *C3*, C-C motif chemokine ligand 2 (*CCL2*), C-C motif chemokine ligand 5 (*CCL5*), C-C motif chemokine receptor 4 (*CCR4*), colony stimulating factor 1 (*CSF1*), C-X-C motif chemokine ligand 10 (*CXCL10*), C-X-C motif chemokine ligand 11 (*CXCL11*), interleukin 1 beta (*IL1β*), *IL8* and interleukin 10 (*IL10*), all of which were highly expressed in AL compared to MM.[23] These findings overlap with the transcriptome profiling identified in the cardiomyocyte population, with implications that need to be further studied in both compartments (the BM niche and the target organ).

Tumour necrosis factor (TNF)

TNF is a group of pro-inflammatory cytokines comprising 19 ligands and 29 receptors, with diverse functions, including immune system regulation through the activation of nuclear factor kappa B subunit 1 (NF-κB) and c-Jun N-terminal kinases (JNK) signalling pathways.[98–100] TNF can stimulate cancer cell growth or act as a tumour suppressor by inducing cell death. One key receptor, CD27, encoded by *TNFRSF7*, is expressed in mature B lymphocytes and is involved in regulating immune response, inflammation and cell survival.[98] It is crucial for B-cell differentiation into plasma cells. Guikema et al. showed that the absence of CD27 expression is linked to MM progression.[101] Gene expression profiling indicates that CD27 expression differs between AL amyloidosis and MM, but not between AL amyloidosis and healthy donors. In AL amyloidosis, CD27-positive PCs were associated with poorer haematological response and worse OS compared to CD27-negative patients.[63,102,103]

Another key receptor, *TNFRSF17* (BCMA), is overexpressed in plasma cells in both MM and AL amyloidosis, contributing to disease pathogenesis.[99,104] Novel immunotherapeutic approaches targeting BCMA in MM are also being investigated for AL amyloidosis.[104,105] Additional TNF receptors, such as *TNFRSF6* (FAS/CD95) and *TNFRSF19L* (RELT), are involved in apoptosis regulation and immune response, with their dysregulation potentially contributing to the development of AL amyloidosis.[98,106–108] Table 4 summarizes the key differences in molecular profiling between AL amyloidosis and MM.

Biological models to study AL amyloidosis

Experimental models are essential for understanding AL amyloidosis pathophysiology and developing targeted therapies. Several models have been proposed; however, each one has its limitations:

- ALMC-1 cell line: The first plasma cell amyloidosis model, ALMC-1, was derived from a BM of a 50-year-old female patient with AL amyloidosis later diagnosed with MM. It naturally secretes amyloidogenic Ig lambda LC, relies on IL-6 for proliferation and exhibits c-MYC amplification, p53 deletion and MAFB overexpression. These cells are hypo-tetraploid, express CD44 and serve as a valuable model for studying disease progression.[29]
- Lentiviral plasma cell model: Pick et al.[109] developed AL LC-producing plasma cell lines using lentiviral vectors containing patient-derived LC sequences. This model suggests that the constitutive expression of amyloidogenic LC alters plasma cell behaviour by inducing intracellular toxicity. This model offers a valuable tool for studying AL pathogenesis and identifying therapeutic targets.
- Non-mammalian models: Organisms like *Drosophila*, zebrafish and *Caenorhabditis elegans* provide insights into disease mechanisms and potential therapeutic approaches. While these models reveal key aspects of AL amyloidosis, they have limitations in replicating the full phenotype of the disease, such as tissue damage and amyloid fibril accumulation. Nevertheless, they serve as complementary tools to mammal studies, enhancing the overall understanding of AL amyloidosis.[51]
- Transgenic mouse models: Ongoing efforts to generate transgenic mouse models for AL amyloidosis have shown that, despite high levels of LC production, the mice do not spontaneously develop AL amyloidosis. To date, none of the transgenic models have achieved the requisite levels of

TABLE 4 Molecular profile comparison: Multiple myeloma versus AL amyloidosis.

	Multiple myeloma	AL amyloidosis
Chromosomal translocations	Among *IGH* translocations in multiple myeloma, t(4;14) is the most frequent (approximately 10% of patients), followed by t(14;16) (approximately 5%). Both are associated with high-risk disease	*IGH* translocations are present in 50%–70% of cases, with t(11;14) being the most common. In daratumumab-treated patients, t(11;14) does not appear to have prognostic significance. The prognostic impact of other *IGH* translocations remains unclear due to their low frequency
Gain of 1q21	Present in 40%–50%, more aggressive tumour growth, increased proliferation	Present in approximately 20%–30% of patients. It is associated with a higher plasma cell burden and concomitant MM
Trisomies/Hyperdiploidy	Very common (40%–60%) and generally associated with a more favourable prognosis compared to non-hyperdiploid MM	Present in 20%–30% of AL patients, associated with higher light chain and plasma cell burdens, and may negatively impact survival
Del 17p/TP53 mutation	Found in up to 10% of MM patients and is considered a high-risk marker associated with poorer prognosis and more aggressive disease course	Observed in 3%–5% of AL patients. While less studied than MM, it appears to have negative prognostic impact
NRAS, BRAF and TRAF genes	Known to be involved in MM progression	Not yet identified in AL amyloidosis
IGLV	IGHV3-30 predominates in MM	Overrepresentation of certain IGLV genes associated with specific organ involvement
DUSP2	Present in MM	Rarely observed in AL amyloidosis
BCL2 family members	Overexpression of BCL2 may promote plasma cell survival. Venetoclax has shown promising results in patients with t(11;14) and high BCL2 expression	Abnormal expressions of BCL2, MCL1 and BCL2L1 may promote plasma cell survival and LC production Venetoclax has induced hematologic remissions in relapsed/refractory patients with t(11;14)
TNFRSF7 (CD27)	Loss of CD27 expression is associated with MM progression	CD27-positive PCs are associated with poorer haematological response and worse overall OS
TNFRSF17 (BCMA)	Overexpressed in AL amyloidosis and MM, contributing to disease pathogenesis	
SNP rs4487645 (G>T)	Associated with the risk of both MM and AL amyloidosis	

Abbreviations: Bcl-2, B-cell leukaemia/lymphoma 2; BCL2L1, BCL2 like 1; BCMA, B-cell maturation antigen; DUSP2, dual specificity phosphatase 2; *IGH*, immunoglobulin heavy chain; IGLV, immunoglobulin variable light; LC, light chain; MCL1, MCL1 apoptosis regulator; MM, multiple myeloma; OS, overall survival; PCs, plasma cells; SNP, single-nucleotide polymorphism.

circulating free LCs necessary to initiate systemic amyloid deposition. The developmental trajectory of mouse models in AL amyloidosis is comprehensively reviewed by the Sirac group.[51]

Unmet needs and future directions

Despite significant progress in understanding the molecular mechanisms underlying AL amyloidosis, many critical gaps remain, limiting our ability to optimize patient outcomes. Existing preclinical models, while invaluable, do not fully replicate the complexity of human disease, particularly the interplay between the BM-derived clonal plasma cells, systemic circulation and target organs. Addressing these gaps is essential for the development of more effective and personalized therapeutic strategies.

Clinical implications and translational research needs

AL amyloidosis research faces major challenges, including a lack of predictive models for organ-specific amyloid deposition. While genetic markers, such as certain IGLV subfamilies, have been linked to cardiac and renal involvement, current models cannot accurately predict organ involvement at early disease stages. Developing robust in vivo models that reflect the heterogeneity of amyloid deposition is crucial. Advances in patient-derived xenografts and three-dimensional models that mimic the BM and organ microenvironments could bridge this gap. Creating transgenic or humanized models capable of recapitulating the full spectrum of tissue involvement in AL amyloidosis would not only accelerate the development of targeted therapies but also provide a platform for testing new drugs in a personalized manner using patient-derived tissues and organoids.

Another emerging area is immune modulation and cell-based therapies, given the immune system's role in amyloid clearance. Interactions between immune cells and amyloid fibrils—through complement activation and macrophage recruitment—offer opportunities to enhance amyloid clearance. Immunomodulatory strategies, including bi-specific antibodies targeting plasma cells, hold promise, while cellular therapies such as Chimeric Antigen Receptor T-cells are now being explored.[110] Further investigation into how these therapies influence the innate immune system could lead to breakthroughs in disease management.

A key unmet need is the integration of biomarkers for real-time disease monitoring. While serum FLC levels and organ-specific markers such as NT-proBNP are widely used, their limitation in capturing disease complexity and predicting long-term outcomes underscores the need for better real-time monitoring tools. A more comprehensive approach leveraging multiomics technologies integrating genomics, transcriptomics, proteomics and epigenetics could improve disease stratification and treatment response assessment. Combining molecular biomarkers with advanced imaging techniques may enable real-time disease tracking, allowing for earlier interventions and personalized treatment adjustments.

Addressing these unmet needs through improved disease modelling, immune-based therapies and biomarker-driven monitoring will be essential in advancing the field of AL amyloidosis toward more precise and effective therapeutic strategies.

CONCLUSION

While substantial progress has been made in understanding the molecular landscape of AL amyloidosis, critical challenges remain in fully translating these discoveries into clinical practice. By addressing unmet needs in early-stage pathogenesis and personalized treatment, and by developing research models, future research has the potential to improve patient outcomes. Close collaboration between the scientific community, industry and global health organizations is essential for driving these advancements forward.

AUTHOR CONTRIBUTIONS

T.Z.-B., E.M., A.D., O.S. and O.H.-R. participated in drafting, reviewing and editing the text, as well as providing critical insights on the content and structure of the review.

FUNDING INFORMATION

The Israeli Ministry of Innovation, Science and Technology (Grant no. 0005792).

CONFLICT OF INTEREST STATEMENT

Eli Muchtar: Protego consultancy fee (paid to institution). Angela Dispenzieri received research funding from Celgene, Millennium Pharmaceuticals, Pfizer and Janssen, and received a travel grant from Pfizer.

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How to cite this article: Zvida-Bloch T, Muchtar E, Dispenzieri A, Shpilberg O, Hershkovitz-Rokah O. The molecular landscape of AL amyloidosis. Br J Haematol. 2025;206(5):1297–1311. https://doi.org/10.1111/bjh.20070