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Review

Virus-like particles of retroviral origin in protein aggregation and neurodegenerative diseases

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Abstract

A wide range of human diseases are associated with protein misfolding and amyloid aggregates. Recent studies suggest that in certain neurological disorders, including Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD) and various tauopathies, protein aggregation may be promoted by virus-like particles (VLPs) formed by endogenous retroviruses (ERVs). The molecular mechanisms by which these VLPs contribute to protein aggregation, however, remain enigmatic. Here, we discuss possible molecular mechanisms of ERV-derived VLPs in the formation and spread of protein aggregates. An intriguing possibility is that liquid-like condensates may facilitate the formation of both protein aggregates and ERV-derived VLPs. We also describe how RNA chaperoning, and the encapsulation and trafficking of misfolded proteins, may contribute to protein homeostasis through the elimination of protein aggregates from cells. Based on these insights, we discuss future potential therapeutic opportunities.

1. Introduction

The conversion of native proteins into amyloid aggregates is associated with over 50 human disorders, including neurodegenerative conditions such as Alzheimer's and Parkinson's diseases, Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) (Knowles et al., 2014; Chiti and Dobson, 2017; Scheckel and Aguzzi, 2018; Louros et al., 2023). A variety of complementary mechanisms play important roles in this process, including amyloidogenic mutations in the genes encoding for the aggregating proteins (Guthertz et al., 2022; De et al., 2015), the age-related accumulation of cellular damage (Niss et al., 2021; Nihei et al., 2020), in particular through inflammatory processes (Cheng et al., 2018; Cascella et al., 2022), the progressive impairment of the protein homeostasis system (Hipp et al., 2019; Thibaudeau et al., 2018; Balch et al., 2008), and the exposure to environmental triggers, such as viral infections and nanoparticles (Michiels et al., 2020; Ezzat et al., 2019; Dong et al., 2023). A common feature of these triggers is catalysis of the aggregation process by reducing the nucleation barrier that separates the native state from the amyloid state, which is a common rate-limiting step (Michaels et al., 2016).

In this review, we focus on a specific class of these triggers - virus-like particles (VLPs) of endogenous origin (Campillos et al., 2006) (Fig. 1). These VLPs are self-assembling protein structures that resemble viruses but lack viral genetic material. VLPs can arise from retrotransposons, particularly long terminal repeat (LTR) elements, and in some cases domesticated transposable elements, including some rare DNA transposon-derived systems. Additionally, endogenous protein assemblies resembling VLPs have evolved from repurposed endogenous retroviral genes, such as Arc, which forms capsid-like structures to mediate intercellular RNA transfer. These endogenous VLPs are composed of solid-like, ordered assemblies that can be transmitted from cell to cell (Erlendsson et al., 2020; Xu et al., 2024) to perform physiological functions, such as mRNA trafficking between neurons (Ashley et al., 2018; Pastuzyn et al., 2018). VLPs can also be released as

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membrane-bound extracellular vesicles (EVs). In either naked or membrane-bound forms, VLPs can be infectious and spread different pathologies depending on the cargo (Pastuzyn and Shepherd, 2017; Segel et al., 2021). In transmissible spongiform encephalopathies (TSEs), for example, about 50 % of RNAs transmitted from cell to cell are transposable elements of possible retroviral origin, or repeats caused by ancient viral infections (Bellingham et al., 2012; Lathe and Darlix, 2020; Akowitz et al., 1994).

The neuronal activity-regulated cytoskeleton-associated protein (Arc), contains a viral group-specific antigen (Gag) sequence element that originates from the Ty3/Gypsy retrotransposon family and is common to Gag polyproteins in retroviruses (Shepherd, 2018). Arc plays key roles in memory and learning through trafficking of α-amino-3--hydroxy-5-methyl-4-isoxazolepropionic (AMPA) type glutamate receptors (Shepherd et al., 2006). The Arc Gag domain forms a virus-like capsid, which encapsulates Arc mRNA and is released in extracellular vesicles (EVs) (Ashley et al., 2018; Pastuzyn et al., 2018). Cell-to-cell mRNA trafficking by Arc VLPs contributes to regulating intercellular synaptic plasticity (Ravens et al., 2024). The VLPs, formed by the paternally expressed gene 10 (PEG10) also mediate mRNA delivery and package PEG10 mRNA in EVs (Segel et al., 2021). Disrupted expression of either Arc or PEG10 may perturb intercellular signaling, which may play a role in several neurological disorders such as Angelman syndrome (Pastuzyn and Shepherd, 2017), Autism Spectrum Disorders (Wilkerson et al., 2018), Alzheimer's disease (Wu et al., 2011; Bi et al., 2018; Landgren et al., 2012), and ALS (Black et al., 2023). The paraneoplastic Ma antigen 2 (PNMA2) protein forms non-enveloped virus-like capsids, injection of which causes memory and learning deficits in mice (Xu et al., 2024). Other viral domain containing proteins were related to neuroinflammation, albeit the direct structural evidence for VLP formation is lacking (Laufer et al., 2009).

Increased expression of endogenous retroviral mRNA and proteins has been observed in protein aggregation diseases (Ezzat et al., 2019; Douville et al., 2011; Sun et al., 2018; Ochoa et al., 2023; Frost and Dubnau, 2024; Schneider et al., 2024), for example in tau pathologies (Sun et al., 2018), such as Alzheimer's disease (Guo et al., 2018a), or in sporadic Creutzfeldt-Jakob disease (Jeong et al., 2010). The aberrant formation of VLPs has been linked with protein aggregation through a variety of molecular processes, including interactions with RNA, liquid-liquid phase separation, and formation of stress granules (Ezzat et al., 2019; Schneider et al., 2024). The co-condensation of VLP-forming proteins and amyloidogenic proteins within liquid-like compartments increases the local concentration of aggregation-prone species, potentially accelerating amyloid fibril formation. The molecular mechanisms of how VLP liquid-like condensates modulates the development of protein aggregation in diseases are not completely understood. The appearance of protein aggregates, for example in early stages of prion disease and sporadic Creutzfeldt-Jakob disease (CJD), decreases the level of AMPA receptors due to overexpression of Arc (Ojeda-Juarez et al., 2022). The infectivity of CJD was related to virus-like particles (Manuelidis, 2007; Manuelidis et al., 2007). VLPs may also co-localise with protein aggregates (Schneider et al., 2024) or interfere with protein homeostasis (Mohan et al., 2024). Alternatively, increased VLP concentrations may induce neuroinflammation (Schneider et al., 2024; Schulz et al., 2023). VLPs or VLP-containing EVs may also facilitate the spread of misfolded protein species (Liu et al., 2021; Chang and Dubnau, 2023).

Here, we explore the molecular mechanisms through which endogenous retrovirus (ERV)-derived VLPs may contribute to the formation and spread of protein aggregates. We discuss the biophysical properties of ERV-derived VLPs, their interactions with protein homeostasis pathways, and potential therapeutic strategies targeting these processes. We focus on the biophysical mechanisms of formation of amyloid fibrils and ERV-derived VLPs, and the possible roles of liquid condensates in these processes. We also outline possible pathways of co-transmission of these particles in the spread of pathology. We finally offer perspectives on the possible exploitation of ERV-derived VLPs to create therapeutic opportunities.

2. VLP formation through liquid-like condensates

2.1. The deposition and condensation pathways of protein aggregation

Aggregation-prone proteins may self-assemble via two main pathways (Fig. 2). In the deposition pathway, misfolding events expose aggregation-prone regions (APRs), which can then give rise to aberrant

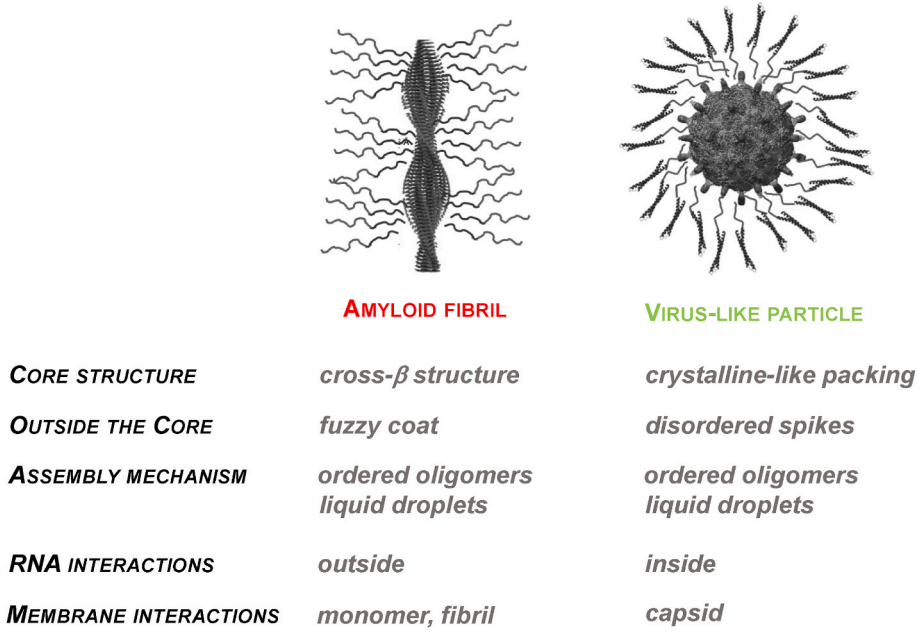

Fig. 1. Characteristic features of amyloid fibrils and VLPs. Amyloid fibrils and VLPs are highly ordered states. RNA modulates amyloid assembly and can either promote or inhibit protein aggregation, while it facilitates VLP formation and becomes encapsulated in the capsid. Membranes can stabilize the monomeric form of the aggregating protein and contribute to the release of VLPs.

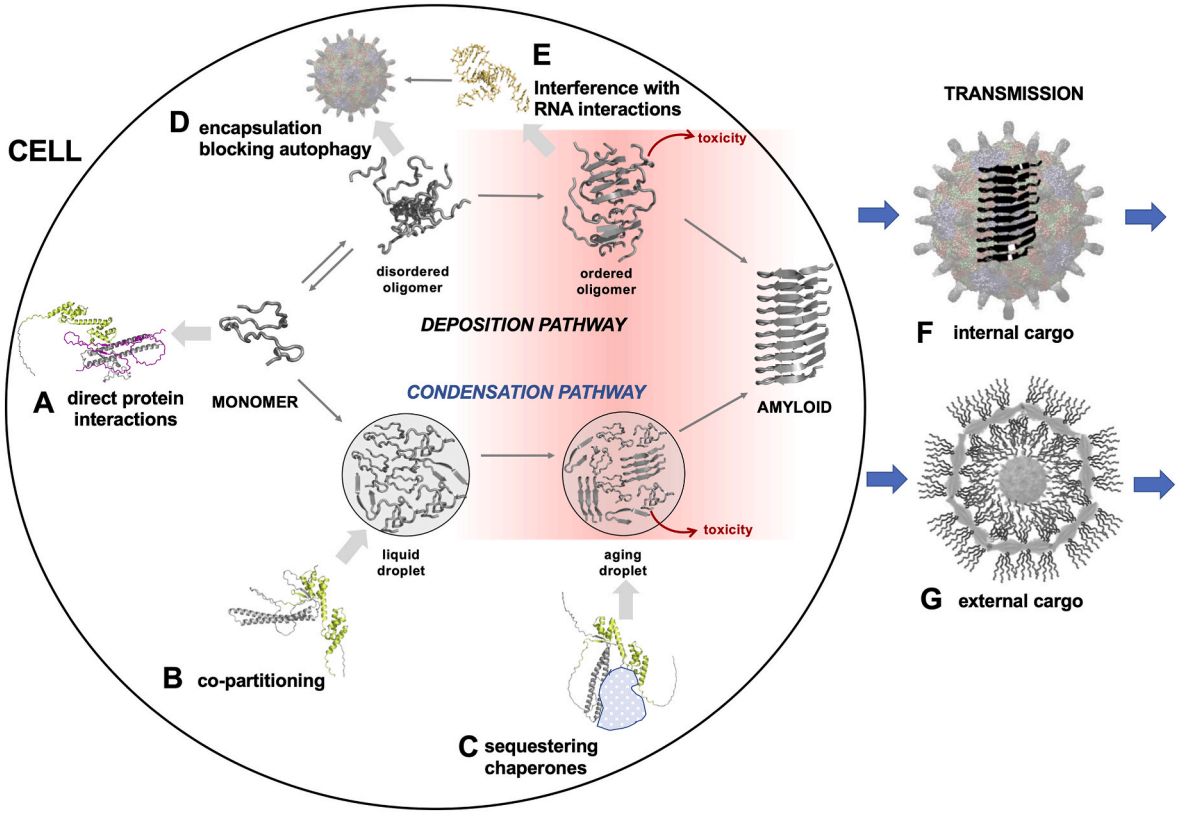

Fig. 2. List of possible mechanisms of interplay between protein aggregation and VLPs. Protein aggregation may take place via two main pathways, the deposition pathway and the condensation pathway. (**A**) **Direct protein interactions.** VLPs may interact with protein monomers and mask their aggregation-prone elements. (**B**) **Co-condensation.** VLP-forming proteins may form liquid-like condensates with aggregation-prone proteins through disordered interactions. These interactions increase the concentration of aggregation-prone elements, while impeding aggregation by inhibiting the conversion into ordered states. (**C**) **Sequestering molecular chaperones.** Condensates containing VLP-forming proteins and amyloid-forming proteins, may also promote the partitioning of molecular chaperones, thus facilitating protein homeostasis. (**D**) **Encapsulating misfolded oligomers.** VLPs may enclose misfolded oligomers and thus block their elimination through degradation pathways. (**E**) **Interference with RNA homeostasis.** VLPs may internalise RNA, thus interfering with RNA homeostasis and its impact on protein aggregation. (**F**) **Transmission within VLPs.** Ordered oligomers or amyloid fragments can be encapsulated and removed from cells. (**G**) **Transmission through the fuzzy coat.** Amyloid fibrils may form fuzzy interactions with the disordered flanking regions of the retroviral domains, and hitchhike on the capsid surface. These interactions are usually sensitive to pH or ionic strength, facilitating disassembly. The viral domain (gag) of the Arc protein is shown green, whereas the interacting human tau (2N4R) in purple, as predicted by AlphaFold3 (Abramson et al., 2024). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

intermolecular interactions (Nelson et al., 2005), leading to the formation of misfolded oligomers (Michaels et al., 2020) and amyloid fibrils (Fitzpatrick et al., 2017). In the condensation pathway, proteins first assemble into dense, liquid-like structures (Patel et al., 2015; Molliex et al., 2015; Ambadipudi et al., 2017; Wegmann et al., 2018; Ray et al., 2020; Hardenberg et al., 2021; Michaels et al., 2023), referred to as droplets, which also contain nucleic acids, lipids and metabolites. While initially these condensates are dynamic, and rapidly exchange their components with their local environment, their dysregulation may induce their structural aging, eventually leading to the irreversible conversion into amyloid fibrils (Alberti and Hyman, 2021; Harrison and Shorter, 2017). Such condensate maturation can be caused by diverse mechanisms, such as perturbed interactions, for example loss of dynamic RNA interactions (Niaki et al., 2020) or network changes (Markmiller et al., 2018; Sui et al., 2020), post-translational modifications (Gwon et al., 2021), compromised molecular chaperone activity (Mateju et al., 2017) or changes in the cellular localization or milieu (Guo et al., 2018b; Alberti and Dormann, 2019; Vendruscolo and Fuxreiter, 2022). The role of the liquid-like condensates in the process of protein aggregation is still debated. One possibility is that the formation of droplets increases the risk of aggregation by increasing the concentration of proteins (Mathieu et al., 2020), which may already be close to their solubility limits (Vecchi et al., 2020). This increases the probability of nucleation by facilitating encounters of APRs (Michaels et al., 2023) in both primary and secondary nucleation (Dada et al., 2023; Shen et al., 2023). Furthermore, the droplets may also stabilize a toxic or aggregation-prone conformation of proteins (Bolognesi et al., 2016; Kanaan et al., 2020) or promote partitioning of factors, such as enzymes catalyzing post-translational modifications, that facilitate aggregation (Wegmann et al., 2018; Monahan et al., 2017). On the other hand, within the droplets, the components interact in a heterogeneous manner, which hinders the formation of ordered assemblies (Wu and Fuxreiter, 2016; Vendruscolo and Fuxreiter, 2021). Such disordered binding within droplets thus may serve to protect proteins from aggregation (Agarwal et al., 2022). For example, droplets formed by α-synuclein may play many different roles (Lipinski et al., 2022). Aggregation and condensation may also be competitive mechanisms, for example in case of the heterogeneous ribonucleoprotein D-like (Batlle et al., 2020). We note that the droplet state is often the physiological form of proteins that are important for functions, such as the regulation of the rates of chemical reactions or gene expression, and the coordination of repair or homeostatic machineries (Lyon et al., 2021). The biophysical properties of the droplet state, such as its dynamics, viscosity or other material properties, are critical for these processes, and thus can be under evolutionary selection (Kirschner and Gerhart, 1998; Fuxreiter and Vendruscolo, 2021).

2.2. Liquid-liquid phase separation may promote the formation of VLPs

Various lines of experimental evidence suggest that, in some cases, the replication compartments of viruses, which may also sequester ribosomes and cellular translation factors, are liquid-like condensates (Zhang et al., 2023; Wu et al., 2022; Geiger et al., 2021; Heinrich et al., 2018). Formation of such compartments can increase the local concentration of replication proteins through liquid-liquid phase separation (Haller et al., 2024). The properties of such condensates are affected by the cellular conditions, in particular stress (Liu et al., 2024). During assembly of viral particles, the disordered segments of the nucleoprotein and phosphoproteins (Communie et al., 2013; Gondelaud et al., 2022) interact through multivalent, fuzzy interactions (Troilo et al., 2018; Bignon et al., 2018; Ivanyi-Nagy and Darlix, 2012). These transient contacts may also lead to the formation of disordered, liquid-like states. In addition, disordered regions also bind RNA in a similar, multivalent fashion, which further facilitates the phase separation process, as was shown for SARS-CoV-2 or mammalian reoviruses (Cubuk et al., 2021; Mitra et al., 2024). Electrostatic interactions with RNA provide further contributions to forming liquid-like condensates (Roden and Gladfelter, 2021). Retroviral proteins may also partition into condensates of other proteins, for example by hijacking transcriptional condensates (Asimi et al., 2022).

Formation of VLPs, similarly to crystallization, requires a homogeneous nucleus with appropriate symmetry. The metastable critical point of liquid-liquid phase separation was shown to modulate the nucleation pathway of crystal formation (ten et al., 1997). In the proximity of critical point, the enhanced density fluctuations reduce the free energy barrier for crystal nucleation, thus increasing the nucleation rates by orders of magnitude (ten et al., 1997). The solvent composition, or the composition of the cellular milieu controls the critical point for liquid-liquid phase separation (Fuxreiter, 2025), and thus the nucleation of virus-like particles.

3. Molecular factors and sequence determinants of protein self-assembly

3.1. Aggregation hot-spots

The properties of amyloid fibrils are determined by the complex interplay between the amyloid core and its flanking regions. The amyloid core contains residues with strong preference for cross-β structures (Sawaya et al., 2007), or sometimes cross-α structures (Tayeb-Fligelman et al., 2017; Xu et al., 2014). The amyloid core is formed by small, dominantly hydrophobic residues (Louros et al., 2020), which can be tightly packed through backbone contacts. The residues can interact in an ordered manner, yet in different registers leading to amyloid polymorphism (Mukrasch et al., 2009; Lovestam et al., 2024; Cao et al., 2019; Tanaka et al., 2004; Krishnan and Lindquist, 2005; Reymer et al., 2014; Louros et al., 2024). Conformational flexibility critically influences formation of polymorphic structures (Frederick et al., 2014; Tanaka et al., 2006) and amyloid nucleation strongly depends on chain dynamics (Scheibel and Lindquist, 2001). The residues flanking the core thus contribute to aggregation (Ulamec et al., 2020). APRs are often embedded in intrinsically disordered regions (IDRs) (Santos et al., 2021), with a composition contrasting that of the IDR sequence (Holehouse and Kragelund, 2024). Due to the conformational freedom of the IDR, the embedded APRs are particularly prone to self-assembly, as observed in case of tau, α-synuclein, or amyloid-β.

During amyloid formation through liquid-like intermediates, the disordered interactions in the liquid condensates gradually convert into ordered interactions of the amyloid state (Vendruscolo and Fuxreiter, 2021). The core residues are prone to form both types of interactions, with preference for the ordered state. In contrast, the flanking residues, which can also sample both ordered and disordered binding modes, exhibit a preference for disordered interactions (Vendruscolo and Fuxreiter, 2022). Therefore, these residues provide the conformational flexibility for the core residues, while promoting the gradual shift towards ordered interactions. Disease-associated missense mutations expand the interaction repertoire of the flanking regions, thus facilitating aggregation without rigidifying the sequence (Vendruscolo and Fuxreiter, 2021). Structurally, metastable, kinked β-structures are characteristic of the condensed state of amyloid-forming proteins (Hughes et al., 2018; Murray et al., 2017).

3.2. Organisation of viral capsids within cellular condensates

Viral capsid assembly within cellular condensates (Zhang et al., 2023; Liu et al., 2024) takes place through multivalent interactions of disordered proteins, which lead to dynamic, liquid-like viral factories (Miller et al., 2010). The biophysical properties of viral condensates are modulated by cellular stress, leading to perturbed interaction networks and formation of more stable replication platforms (Zhang et al., 2023). Cryo-electron tomography indicated the formation of heterogeneous species, including single layer early intermediates, as well as double layer mature products within cellular condensates (Liu et al., 2024). Both the core and the virion species were observed with and without RNA, which were bound in a disordered manner. Viral proteins undergo major conformational changes during capsid assembly (Zhang et al., 2023; Liu et al., 2024), which is facilitated by their high concentration and conformational freedom within the condensate. In addition, RNA also contributes to structural organization and shape of VLPs (Liu et al., 2024).

Gag domain-containing retroviral proteins, such as PEG10 or retrotransposon Gag-like 8 (RTL8) were observed to partition into stress granules (SGs) (Mohan et al., 2024). SGs contain translationally-stalled mRNAs and RNA-binding proteins, along with many other components ranging from enzymes to nuclear transport proteins, and form in response to stress (Mohan et al., 2024). Stress conditions alter their interaction with UBQLN2, a major component of the protein quality control (PQC) system, which shuttles ubiquitinated clients for proteasomal degradation. Perturbed interactions between PEG10, RTL8 and UBQLN2 also alter stress granule dynamics and composition, affecting other components of the homeostasis system. PEG10 forms virus-like particles under physiological conditions, which were observed within SGs in the cellular context (Mohan et al., 2024). This is in line with the heterogeneity of viral protein condensates as well as with previous observations on the heterogeneity of SGs (Parker et al., 2025; Youn et al., 2019; Yang et al., 2020).

4. Beyond the structured assembly

4.1. The fuzzy coat of amyloid fibrils

The highly ordered structural core of amyloid fibrils is often flanked by disordered regions that may be detectable using cryo-electron microscopy (cryo-EM) (Fitzpatrick et al., 2017; Krishnan and Lindquist, 2005; Milanesi et al., 2025; Faidon et al., 2023). In case of tau, approximately 300 residues at the N- and C-terminus remain unstructured and form a fuzzy coat around the cross-β core (Steiner et al., 1990; Wischik et al., 1988) (Fig. 1). The fuzzy coat thus serves as a brush, which shapes the mechanical properties of the fibril (Mukhopadhyay et al., 2007) (Tompa, 2005; Wegmann et al., 2013). The mechanical properties of the coat are modulated by the pH, ionic strength and electrostatic properties of the cellular environment. In turn, the coat morphology controls the stability and adhesiveness of the fibril (Wegmann et al., 2013).

The fuzzy coat plays a role in interactions of the amyloid with other cellular components, for example with molecular chaperones (Ghosh et al., 2024). In the case of α-synuclein, the BRICHOS domain of the lung surfactant protein (proSP-C) binds to the C-terminus of the fuzzy coat and protects from secondary nucleation. The fuzzy coat may also

interact with RNA cofactors, which promote fibril formation through modulating the electrostatic forces (Cooney et al., 2023), and regulate the interactions with lipids and cytoskeletal filaments, as in the case of tau (Steiner et al., 1990; Wischik et al., 1988; Wegmann et al., 2013).

4.2. VLP spikes

VLPs are decorated with 5–10 nm long protrusions, which are structurally heterogeneous (Ke et al., 2024; Henderson et al., 2020) and often cannot be fully resolved structurally (Zhang et al., 2023; Liu et al., 2024; Zhu et al., 2023) (Fig. 1). In viruses, the spikes contain glycosylated precursor proteins and signal peptides, which are responsible for cell entry (Eilon-Ashkenazy et al., 2024). The conformational heterogeneity of the spikes enables variable binding modes to their receptors increasing their adaptability (Yang et al., 2024). In case of SARS-CoV2 for example in the range of conformational states involve open, closed, and locked forms representing the pre- and pro-fusion events (Qu et al., 2022). The spikes are often formed by coiled-coiled domains, which emerge from the center of the capsomer (Erlendsson et al., 2020). Conformational transitions of the spikes are enabled by allosteric couplings between the receptor binding domain and the base of the spike (Ke et al., 2024; Henderson et al., 2020). The spikes play a role in virus assembly, enabling the switch from single layered to double layered particles (Sutton et al., 2020). The spikes protruding inwards may also contribute to RNA packaging (Erlendsson et al., 2020). Spike dynamics is modulated by membrane interactions (Zhang et al., 2025).

5. Interactions with RNA and cell membranes

5.1. RNA interactions and chaperoning

RNA binding is a common interface between amyloids and VLP-forming proteins. More than 20 years ago, the role of prion protein (PrP) in RNA binding and chaperoning was identified (Gabus et al., 2001). Binding of HIV-1 RNA to PrP induced the formation of condensed nucleoprotein structures, similarly to those which were observed with retroviral nucleocapsid proteins. Furthermore, PrP also promoted RNA dimerization and tRNA annealing to the 5' primer binding site mimicking virus assembly, similarly to the Ncp7 nucleocapsid protein in HIV-1 replication (Gabus et al., 2001). These observations may indicate that the prion protein is multifunctional and also plays a role in nucleic acid metabolism. These results suggest the presence of particular sequence features that enable both amyloid formation and RNA chaperoning (Lathe and Darlix, 2020). Along these lines, the N-terminus of PrP is intrinsically disordered and positively charged, which is characteristic to many RNA chaperones (Tompa and Csermely, 2004; Calabretta and Richard, 2015) and this polybasic region is evolutionary conserved. Nucleic acid binding to the IDR induces refolding of PrP, which propagates into the aggregating C-terminal region. The IDR is essential for the formation of PrP liquid condensates, which on the other hand may promote PrP aggregation (Kostylev et al., 2018). PrP, whose functional properties in many aspects are similar to Gag proteins (Lathe and Darlix, 2020), not only binds, but also traffics nucleic acids (Bellingham et al., 2012), which in turns leads to the activation of TEs. Recently, a bacterial RNA chaperone Hfq was also identified as amyloid forming (Turbant et al., 2021). Furthermore, amyloid aggregates may also sequester RNA (Rupert et al., 2023).

5.2. RNA contributes to the condensation of VLP-forming and aggregation-prone proteins

RNA promotes formation of cellular condensates formed by both VLP-forming and amyloid-prone proteins through interactions with prion-like, low-complexity and intrinsically disordered proteins (Gitler and Shorter, 2011), such as TDP-43 (French et al., 2019), FUS (Monahan et al., 2017), hnRNPA1 (Kim et al., 2013), TIA-1 (Mackenzie et al., 2017) that are associated with neurological disorders. RNA may facilitate condensation through polyanionic effects, as in case of tau (Ambadipudi et al., 2017; Zhang et al., 2017), while phosphorylation impedes tau coacervation and promotes its aggregation (Hochmair et al., 2022). hnRNPA1 aggregation is modulated by RNA in a concentration-dependent manner (Morelli et al., 2024). While at low RNA concentration condensation takes place, which protects from aggregation, at increased RNA concentrations a re-entrant phase transition promotes aggregation. Thus, RNA can play dual roles in protein aggregation, as was also observed for α-synuclein (Lipinski et al., 2022). At the same time, the condensates of nucleocapsid proteins may partition RNA, which in turn promotes capsid assembly (Guseva et al., 2020). Thus, RNA may facilitate co-condensation of VLPs and amyloid-prone proteins, while interactions with RNA can modulate the formation of solid-like higher-order structures, capsids or amyloid aggregates.

5.3. Cell membrane properties contribute to amyloid aggregation and promote viral capsid assembly

Cell membrane properties and integral membrane proteins strongly affect amyloid aggregation and toxicity. APRs may establish dynamic interactions with the lipid surface (Fusco et al., 2014), which modulates their exposure through composition (Sanguanini et al., 2020; Man et al., 2021) or membrane curvature (Middleton and Rhoades, 2010; Kenyaga et al., 2022). Membrane associated proteins, such as apolipoproteins may interfere with APR exposure and affect aggregation kinetics (Verghese et al., 2013; Liu et al., 2017). Likewise, signaling molecules (Choong et al., 2023) or cholesterol (Habchi et al., 2018) induce aggregation through altering membrane properties (Habchi et al., 2018; Limbocker et al., 2019).

Similarly, cell membrane interactions are critical for assembly of VLPs. Proteins, such as the I-BAR protein IRSp53, which modifies membrane curvature contributes to the release of HIV VLPs (Inamdar et al., 2021) and EVs (Ravens et al., 2024; de Poret et al., 2022). Retroviruses interact with the ESCRT machinery, which are required for VLP release and the seeding of capsid assembly occurs at membranes, possibly through a charge interaction (Freed, 2015).

6. Transmission mechanisms

Accumulating experimental evidence indicates the roles of EVs in the spread of pathology in neurodegenerative disorders (Budnik et al., 2016; Graykowski et al., 2020). For example, infectious CJD particles that lack prion protein itself, instead were enriched in viral peptides (Kipkorir et al., 2014). From infectious CJD particles 25 nm virus-like particles were isolated, which did not show any PrP antibody binding (Manuelidis et al., 2007; Silveira et al., 2005). Infectivity was related to the encapsulated RNA, suggesting that VLPs were responsible for the spread of pathology (Manuelidis, 2007). Intriguingly, these VLPs were of retroviral origin and found to encapsulate long RNAs (Akowitz et al., 1994).

The direct roles of VLPs and VLP-containing EVs in the spread of protein aggregates were also recently observed (Chang and Dubnau, 2023; Liu et al., 2023). Upon heat-stress, VLPs were found to co-localise with protein aggregates near mitochondria, independently of ribonucleoprotein granules (Schneider et al., 2024). VLP co-localization may also involve some components of the protein quality control (PQC) machinery (Mohan et al., 2022). Induced formation of VLPs, for example caused by mdg4-ERV (gypsy) expression in surface glia, triggers intercellular spread of TDP-43 proteinopathy even at physiological levels of human TDP-43 (Chang and Dubnau, 2023). Interestingly, aggregated TDP-43 alone is not sufficient to transmit ALS or FTD (Polymenidou and Cleveland, 2011). These experiments suggest that in addition to the positive feedback, viral transmission may also play a role in TDP-43 pathology spread (Chang and Dubnau, 2023). Along these lines, pathological tau spread is increased by endogenous retrovirus envelopes belonging to four different clades (Liu et al., 2023).

Various neurological disorders have been associated with elevated Arc levels, such as Autism Spectrum Disorder (ASD) (Wilkerson et al., 2018), Angelman syndrome (Pastuzyn and Shepherd, 2017) and Alzheimer's disease (AD) (Wu et al., 2011; Bi et al., 2018; Landgren et al., 2012). Arc levels are also upregulated by heat-shock and suppress the expression of heat shock proteins (Park et al., 2019). Appearance of amyloid-β, tau, prion, and α-synuclein oligomers considerably increase Arc levels and thereby reduce metabotropic glutamate receptors (Ojeda-Juarez et al., 2022). Similarly, pathogenic tau also increases Arc levels in a *Drosophila* Alzheimer's model, in particular those of multimeric species (Schulz et al., 2023). Recently, Arc has been implicated in the transmission of pathogenic tau species (Tyagi et al., 2024). Arc directly interacts with tau, and intercellular tau transmission was abrogated in Arc knock-out mice. These experiments raise the possibility that protein aggregates may serve as a cargo of the retroviral VLPs, which contribute to the spread of pathology.

7. Molecular mechanisms of interplay between VLPs and protein aggregates

VLP-forming proteins may interfere with different stages of both the deposition and condensation pathways, as well as the transmission of aggregation intermediates and products (Fig. 2).

7.1. Masking aggregation-prone elements

Direct protein binding may involve motifs, with a preference for β-conformation, thereby impeding their self-assembly (Fig. 2A). This process was observed in case of Arc and tau, where direct protein binding was experimentally demonstrated (Tyagi et al., 2024). Molecular simulations suggested the formation of mixed β-sheets between Arc and tau, which may limit tau self-assembly into the amyloid form. Aggregation-prone elements can also form dynamic, heterogeneous interactions leading to the formation of condensates (Vendruscolo and Fuxreiter, 2021). Multivalent interactions may also be formed between the disordered retroviral domains and the regions flanking the amyloid core residues (Bignon et al., 2018), which may compete with amyloid-like self-assembly (Fig. 2B).

7.2. Interference with protein and RNA homeostasis

Retroviral domains may co-condense with aggregation-prone proteins and components of the PQC system, as it was observed in case of PEG10 (Mohan et al., 2024) (Fig. 2C). This process may facilitate quality control and delay aging in condensates. On the other hand, their interactions may also suppress chaperone activity, through inhibiting the binding of HSF1 to the heat shock element in gene promoters, resulting in reduced induction of Hsp27 and Hsp70 mRNAs (Park et al., 2019). VLPs may also encapsulate misfolded protein intermediates or oligomers through disordered interactions and disable their recognition by the autophagy system (Fig. 2D). VLPs may also encapsulate RNA (Ashley et al., 2018; Pastuzyn et al., 2018), which perturb the homeostasis of retroviral RNA (Fig. 2E). RNA plays important roles in protein aggregation through direct interactions with the aggregation-prone regions or promoting co-condensation and formation of dynamic assemblies (Niaki et al., 2020; Prince et al., 2023; Murakami et al., 2015).

7.3. Pathology spread

The nanocarrier function of VLPs (Li et al., 2024) can also be exploited by oligomers or amyloid fragments. Various lines of experimental evidence indicates that the presence of protein aggregates increases the amount of VLPs (Ojeda-Juarez et al., 2022; Schulz et al., 2023), which in turn facilitate transmission of pathology (Chang and Dubnau, 2023; Liu et al., 2023; Tyagi et al., 2024). Transmission can take place via the encapsulation of the amyloid-like fragments together with RNA through direct protein-protein or protein-RNA interactions (Fig. 2F). Another possibility is that amyloid fragments serve as an external cargo of the VLPs through polyelectrostatic interactions with the fuzzy coat (Wegmann et al., 2013) (Fig. 2G). Due to their sensitivity to pH and ionic strength, amyloid seeds can be released without capsid disassembly.

8. Towards therapeutic opportunities

VLP-forming proteins are associated with a wide range of neurological disorders (Frost and Dubnau, 2024; Ochoa Thomas et al., 2020; Payer and Burns, 2019; Jonsson et al., 2020; Pandya et al., 2021). Here we discuss the molecular mechanisms by which these proteins may contribute to preventing protein aggregation, which may offer therapeutic opportunities. Antiviral drugs, which have been tested for amyloid-β aggregation in Alzheimer's disease (Wozniak et al., 2011; Hui et al., 2020) targeted neuroinflammation or β-secretase levels. Therefore, the small molecules mentioned here are related to some of the outlined mechanisms but have not applied yet to interfere with aggregation through VLP-associated mechanisms. In addition, we note that some of the small molecules investigated so far, such as 100058-F4, may appear as Pan-Assay Interference (PAIN) compounds, which are identified as false positives in high-throughput screens (Baell and Walters, 2014; Baell, 2016; Baell and Holloway, 2010). These molecules may impact various pathways and may not be specific to VLP-associated mechanisms. Nevertheless, outlining the possible mechanisms may provide perspectives for future therapeutic opportunities.

8.1. Stabilising native monomers

Disordered retroviral sequences can establish dynamic, multivalent interactions with the disordered regions embedding APRs (Ulamec et al., 2020; Santos et al., 2021). Such fuzzy assembly, which maintains conformational heterogeneity and dynamics of the amyloid-forming monomeric protein, prevents conversion into more ordered aggregates. Thus, stabilisation of the disordered native form of aggregation-prone proteins (Fig. 3A) by small molecules may offer a therapeutic strategy. This approach was applied to block amyloid β (A β) aggregation (Lohr et al., 2022; Heller et al., 2020) by increasing the entropy of binding, which is modulated by small molecules (Heller et al., 2017). We note, however, that compounds targeting disordered proteins may be associated with increased risk of promiscuity (Baell, 2016).

8.2. Stabilising condensates

The liquid-like droplet state has a dual role in protein aggregation, as it both increases the concentration of the APRs and opposes their ordered assembly. Thus, stabilising the liquid-like condensed state may be useful against aggregations, as in case of α-synuclein (Dada et al., 2024). The interaction between aggregation-prone regions with retroviral domains can facilitate droplet formation through disordered interactions (Fig. 3B), which may prevent further ordering. By increasing the condensate stability, the aggregation-prone protein can be confined in the condensate thus inhibiting the spread of the pathology seeds.

8.3. Interference with cellular homeostasis

Through co-condensation, retroviral domains increase concentration of PQC components in liquid-droplets of aggregation-prone proteins (Fig. 3C). Thus, destabilising the interactions between VLP proteins and PQC components can increase the availability of PQC for misfolded proteins. Another approach to improve the efficiency of the cellular homeostasis system is to inhibit encapsulation of misfolded oligomers, which otherwise may limit the recognition of early-stage aggregates by the homeostasis system. This mechanism may be achieved by destabilising the interactions between aggregate oligomers and VLPs. A further

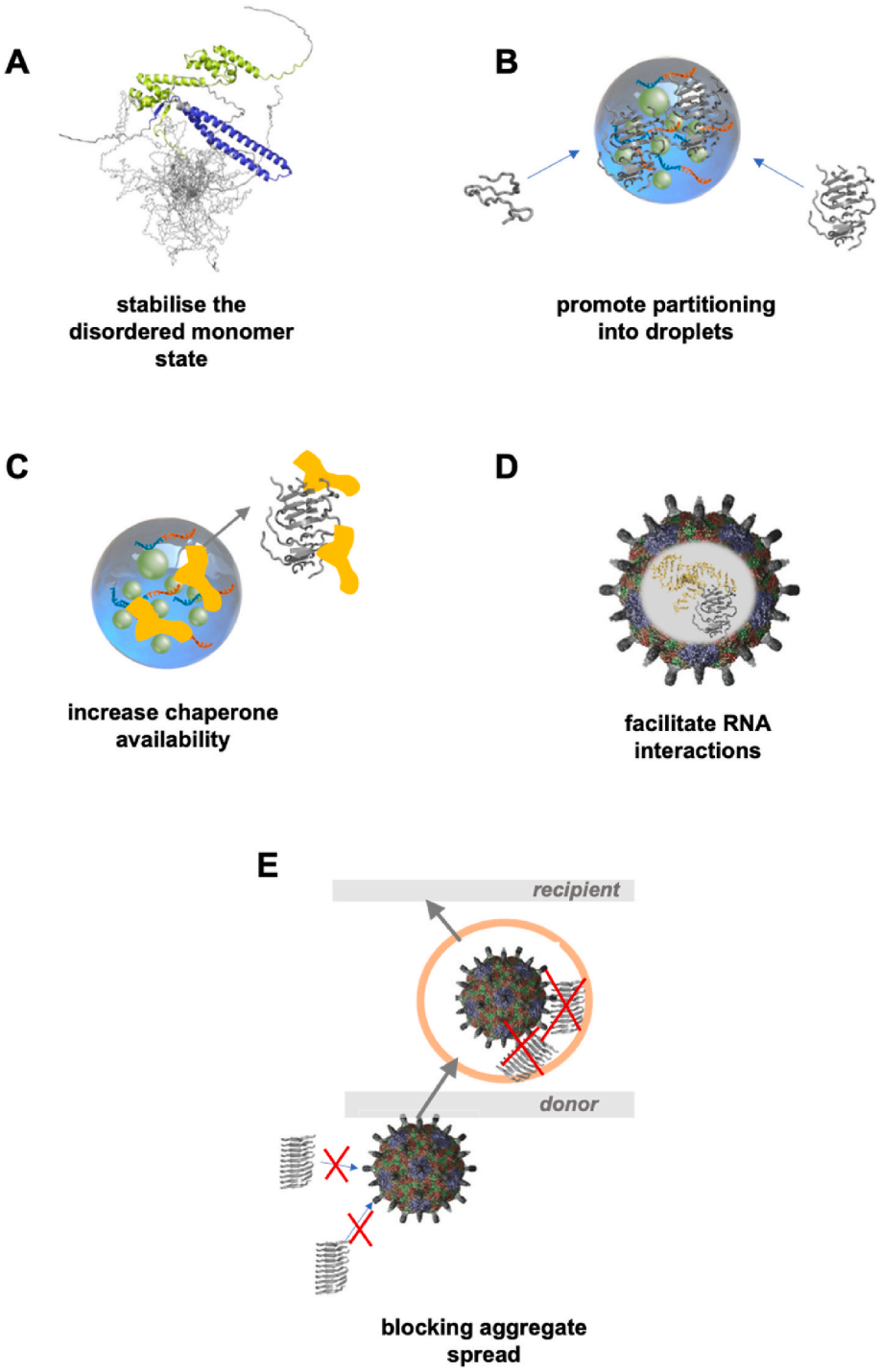

Fig. 3. Possible therapeutic applications of VLP-forming proteins in protein aggregation diseases. (**A**) **Disordered protein interactions with the monomeric state.** The self-assembly of the aggregation-prone elements can be inhibited by competitive interactions with the disordered sequences of the VLP forming proteins. The gag domain is shown by green. (**B**) **Partitioning into condensates.** Liquid-like condensates of VLP-forming proteins may impede the conversion of disordered monomers to misfolded oligomers or trap partly ordered oligomeric states. (**C**) **Increasing availability of PQC components.** Destabilising the interactions between VLP proteins and molecular chaperones or other PQC components may increase their availability for misfolded proteins and promote cellular homeostasis. (**D**) **Facilitating RNA interactions.** VLPs encapsulate RNA, thus limiting the aggregation of the protein cargo. (**E**) **Blocking aggregate spread.** Destabilising interactions between amyloid fibrils and capsid spikes can block transmission of seed-competent species and pathology spread. We note that the molecular mechanisms through which VLP-forming proteins contribute to decreasing protein aggregation can be modulated by small molecules for therapeutic interventions. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

opportunity along this line is to interfere with RNA interactions of VLPs by small molecules or RNA aptamers to facilitate dynamic interactions with aggregation-prone regions (Fig. 3D).

8.4. Blocking the spread of pathology

Inhibiting the interactions between aggregates with VLPs (Fig. 3E) by small molecules may reduce the transmission of seeding-compatible

oligomers between cells and contributes to blocking pathology spread. Murine leukemia virus (MLV) protease inhibitors Amprenavir and Atanazavir, for example, were shown to significantly reduce the spread of Sup35 NM aggregates (Liu et al., 2023). Furthermore, Amprenavir-treatment strongly reduced aggregate induction in recipient cells (Liu et al., 2023). On the other hand, strengthening amyloid-VLPs interactions may help the clearance of misfolded proteins from the cell and their recognition by components of the extracellular homeostasis (Wilson et al., 2023). The interactions through the fuzzy coat can be modulated through pH or highly charged compounds. It also remains to be investigated whether a VLP-bound fibril (Fowler et al., 2025) is more efficiently recognised by the autophagy machinery.

9. Conclusions and Outlook

Proteins exhibit complex, and tightly regulated phase properties in the cellular environment, including the formation of amyloid fibrils, liquid-like condensates and virus-like particles. A wide range of human diseases are associated with the dysregulation of these phase properties. Several VLP-forming proteins of retroviral origin are encoded by the human genome, although most are repressed by healthy cells. When they escape control, however, their aberrant expression may contribute to protein aggregation disorders. At the same time, VLPs may assist protein homeostasis through masking aggregation-prone regions, stabilising condensates or contributing to clearance of amyloid fragments from cells. Some of these biophysical mechanisms can potentially be modulated by small molecules. Blocking the pathology spread also opens an exciting new avenue to interfere with pathological aggregation. We expect that a more extensive elucidation of these mechanisms will offer novel therapeutic opportunities towards a wide range of neurological disorders.

CRediT authorship contribution statement

Serena Carra: Writing – review & editing, Investigation, Funding acquisition. **Balazs Fabian:** Writing – review & editing, Investigation. **Hamed Taghavi:** Investigation. **Edoardo Milanetti:** Investigation. **Valeria Giliberti:** Investigation. **Giancarlo Ruocco:** Writing – review & editing, Conceptualization. **Jason Shepherd:** Writing – original draft, Conceptualization. **Michele Vendruscolo:** Writing – original draft, Conceptualization. **Monika Fuxreiter:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Funding acquisition, Conceptualization.

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