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REVIEW

Suppression and dissolution of amyloid aggregates using ionic liquids

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Abstract

Amyloid aggregates are composed of protein fibrils with a dominant β-sheet structure, are water-insoluble, and are involved in the pathogenesis of many neurodegenerative diseases. Development of pharmaceuticals to treat these diseases and the design of recovery agents for amyloid-type inclusion bodies require the successful suppression and dissolution of such aggregates. Since ionic liquids (ILs) are composed of both a cation and anion and are known to suppress protein aggregation and to dissolve water-insoluble compounds such as cellulose; they may also have potential use as suppression/dissolution agents for amyloid aggregates. In the following review, we present the suppression and dissolution effects of ILs on amyloid aggregates so far reported. The protein–IL affinity (the ability of ILs to interact with amyloid proteins) was found to be the biochemical basis for ILs' suppression of amyloid formation, and the hydrogen-bonding basicity of ILs might be the basis for their ability to dissolve amyloid aggregates. These findings present the potential of ILs to serve as novel pharmaceuticals to treat neurodegenerative diseases and as recovery agents for various amyloid aggregates.

Keywords Amyloid aggregates · Suppression · Dissolution · Ionic liquids · Protein–IL interaction · Solution structure

Abbreviation

[emim]	1-Ethyl-3-methylimidazolium
[bmim]	1-Butyl-3-methylimidazolium
[hmim]	1-Hexyl-3-methylimidazolium
[omim]	1-Methyl-3-octylimidazolium
[Bzmim]	1-Benzyl-3-methylimidazolium
[eDmim]	1-Ethyl-2,3-dimethylimidazolium
[bpyr]	*N*-Butyl-3-methyl-pyridinium
[Phemim]	1-Phenylpropyl-3-methylimidazolium
[dBmim]	1,3-Dibutylimidazolium
[bDmim]	1-Butyl-2,3-dimethylimidazolium
[TMG]	Tetramethylguanidium
[Tea]	Triethylammonium
EAN	Ethylammonium nitrate
PAN	Propylammonium nitrate
BAN	Butylammonium nitrate
MEOAN	2-Methyloxyethylammonium nitrate
[Ac]	Acetate
[H_2PO_4]	Phosphate
[HSO_4]	Hydrogen sulfate
[Tfac]	Trifluoroacetate
[La]	Lactate
[Tf]	Triflate
[Ms]	Mesylate
[BF_4]	Tetrafluoroborate
[PF_6]	Hexafluorophosphate
[TFSI]	Bis(trifluoromethanesulfonyl)imide
[FSI]	Trifluoromethanesulfonate
[CH_3SO_4]	Methylsulfonate
[SCN]	Thiocyanate
[NO_3]	Nitrate
FTIR	Fourier transform infrared
ThT	Thioflavin T
CD	Circular dichroism
CR	Congo red
ANS	8-Anilinonaphthalene-1-sulfonic acid
TEM	Transmission electronic microscopy
SEM	Scanning electron microscope
EM	Electron microscope
AFM	Atomic force microscope
DLS	Dynamic light scattering

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Introduction

Amyloid aggregates are composed of protein fibrils with a dominant β-sheet structure and are formed by ordered aggregation of misfolded proteins. Such aggregates are involved in the pathogenesis of many neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, and are transported to amyloid-type inclusion bodies in response to the overexpression of recombinant proteins (De Groot et al. 2009; Singh et al. 2015). It has been suggested that organic compounds with low formula weights, such as guanidine salts and dimethyl sulfoxide (DMSO), can suppress the formation of amyloid aggregates by dissolving them (Singh et al. 2015; Meersman and Dobson 2006). Electrostatic interactions between protein side chains, such as salt bridges, can influence the amyloid stability by the addition of organic compounds (Shammas et al. 2011). Besides, the basicity of the –S=O group in DMSO may disrupt the intermolecular hydrogen bonding (H-bonding) (Hirota-Nakaoka et al. 2003). Amyloid stability is thought to be effectively controlled by the application of compounds that destabilize these intermolecular interactions such as H-bonding and electrostatic/hydrophobic interactions between proteins, thereby aiding in the suppression and dissolution of amyloid aggregates.

Ionic liquids (ILs) comprising a cation and an anion have shown unique physical and chemical properties, such as negligible vapor pressure and high miscibility with other liquids (Hayes et al. 2015). ILs can be varied to produce solvents with different chaotropic and kosmotropic properties, and these properties are critical in determining the aqueous solubility and protein stability of the solute (Zhang and Cremer 2006). Thus, aqueous mixtures of proteins and ILs play an important role in protein engineering applications, such as protein storage media and biocatalysts, and in the pharmaceutical and biomedical sciences (Greaves and Drummond 2015; Benedetto and Ballone 2015a, b; Egorova et al. 2017). An intriguing feature of aqueous IL solutions is that some ILs cause protein unfolding (Tietze et al. 2013), while others positively influence protein refolding (Summers and Flowers II 2000; Takekiyo et al. 2012). Also intriguing is that the dissolution and regeneration of cellulose and aggregated recombinant proteins have been demonstrated using ILs (Hauru et al. 2012; Fujita et al. 2016). These features imply that ILs may destabilize amyloid aggregates, as the formation and stability of these aggregates are dependent upon the same intramolecular forces present in amyloid aggregates (H-bonding and electrostatic/hydrophobic interactions).

In the following review, we present current information regarding the suppression/dissolution effects of aqueous ILs on amyloid aggregates in solution, giving consideration to protein–IL interactions and solution properties of this media.

Interactions between ionic liquids and proteins

Protein–IL interactions have been the subject of intensive study, primarily the use of ILs as solvents for biochemical reactions such as protein folding/unfolding and protein aggregation (Zhang and Cremer 2006; Patel et al. 2014; Benedetto and Ballone 2015a, b). In fact, protein–IL interactions involving ethylammonium nitrate (EAN) and 1-ethyl-3-methylimidazolium chloride demonstrated a positive effect on protein renaturation (Summers and Flowers II 2000; Tischer et al. 2014). To understand the mechanisms of protein structural changes in aqueous IL solutions, we must first understand protein–IL interactions.

The interactions between human serum albumin and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) have a denaturing effect, and protein–choline dihydrogen phosphate ([Chl][dhp]) interactions have a stabilizing effect (Akdogan et al. 2011). When bovine serum albumin is combined in aqueous solution with imidazolium-based ILs, these cations localize around the hydrophobic residues such as Phe and Leu, and the NO_3^- anion strongly interacting with the protein, by entering the protein interior and disrupting its α-helical structure (Shu et al. 2011). Imidazolium-based ILs with longer alkyl chains have been demonstrated to preferentially interact with hydrophobic moieties, resulting in serious distortions in the protein conformation (Silva et al. 2014). Recently, interaction sites of protein with ILs in concentrated solution have been reported (Takekiyo et al. 2015, 2016; Yoshimura et al. 2016). For instance, [bmim][SCN] interacts with proteins, primarily at Lys and Arg residues, and a higher quantity of these residues induced the suppression of intermolecular β-sheet formation due to the specific amino acid residue–IL interaction (Takekiyo et al. 2015). The interaction sites of strong kosmotropic ions such SCN^- anion with proteins in concentrated aqueous media are consistent with those in the crystalline state (Hamiaux et al. 1999; Vaney et al. 2001), because the protein–kosmotropic ion interactions are stronger than those of the chaotropic ions.

Based on these results, protein–IL interaction depends on a variety of factors that induce changes in protein free energy and the cation and anion species of ILs, as well as their position in the Hofmeister series (Zhang and Cremer 2006). These factors play important roles in protein stability. Some previously determined interaction sites in proteins with ILs dissolved in aqueous solution are summarized in Table 1.

Liquid nano-heterogeneity and protein state in ionic liquid solutions

In addition to protein–IL interactions, the effect of ILs on protein stability is also a function of their liquid structure. IL solutions of $x > 20$ mol% IL often induce formation of unique

Table 1 Interaction sites of proteins with ionic liquids

Ionic liquids	Interaction sites	Methods	References
[dBmim][Cl]	Phe, Ala, Leu, Val, and Ser residues	Molecular docking	Shu et al. 2011
[bmim]-based ILs	Phe, Leu, Val, and Ser residues (NO_3^-: disruption of α-helix)	Molecular docking	Shu et al. 2011
[bmim][SCN]	Lys, Arg, and Glu residues	FTIR	Takekiyo et al. 2015
[bmim][Cl]	Phe, Tyr, and Pro residues	FTIR	Yoshimura et al. 2016
EAN	Ala and Val residues	FTIR	Takekiyo et al. 2016
PAN	Ser, Ala, Lys, Ile, and Val residues	FTIR	Takekiyo et al. 2016

protein states, such as amyloid-type aggregation and helical structure (Takekiyo et al. 2013; Weaver et al. 2012), and it has been suggested that such unique protein states in IL solutions are strongly related to the unique liquid structure with heterogeneous domains (Takekiyo et al. 2014).

It is known that ILs adopt a nano-heterogeneous structure, with a polar domain arising from the interaction of the IL's ionic parts, and a nonpolar domain containing the alkyl chains (Hayes et al. 2015). These binary solutions formed IL-aggregated structures that are surrounded by bulk water molecules under water-rich conditions (lower nano-heterogeneity) (Jiang et al. 2007). However, under IL-rich conditions, the water molecules are scattered in the polar domains and self-assemble in the ILs (higher nano-heterogeneity) (Jiang et al. 2007). Moreover, an increase in alkyl chain length results in an increase in nano-heterogeneity (Hayes et al. 2015). It has been suggested that proteins in IL solutions of 70 vol% are hydrated by water molecules surrounded by IL layers (Tietze et al. 2013). Related to this, a decrease in the cationic alkyl chain length of imidazolium-based ILs causes an increase in the protein size at which protein aggregation occurs, suggesting that changes in the alkyl chain length may control the size at which a specific protein forms aggregates under these conditions (Takekiyo et al. 2014). Thus, the relationship between the size of the water domains and the proteins in solution may allow control of amyloid-type aggregation of proteins in concentrated solutions.

Increasing the proportion of ILs to water molecules induces low polarity of the resulting liquid. The ability of aqueous IL solutions to induce helix formation is similar to alcohol denaturation (Takekiyo et al. 2013, 2017a). The effects of alcohols on proteins are shown to arise from their low polarity; low polarity weakens the hydrophobic interactions that stabilize the compact native structure of proteins, but simultaneously strengthens electrostatic interactions, thus stabilizing secondary structures, particularly the α-helix (Shiraki et al. 1995; Luo and Baldwin 1997). The dielectric constant of pure ILs is low ($\varepsilon = 10\sim15$) (Weingärtner et al. 2001), as is the case for 2,2,2-trifluoroethanol (TFE) ($\varepsilon = 27.1$) (Hong et al. 1999). As such, ILs with low polarity may cause the enhancement of protein intramolecular H-bonds. Thus, the solution property (nano-heterogeneity structure/water hydration and low polarity) acts cooperatively in the helix-forming ability of concentrated IL solutions (Takekiyo et al. 2013, 2017a).

Suppression of amyloid aggregation using ionic liquids

It was known that amyloid stability is affected by the addition of organic compounds, and the interaction between protein and organic compounds can suppress the formation of amyloids (Arora et al. 2004; Shammas et al. 2011). Trimethylamine N-oxide inhibits amyloidogenesis after lysozyme unfolding (Wawer et al. 2014). Besides, indole-3-carbinol interacts with hydrophobic residues such as Trp, Ile, and Ala residues in lysozyme and demonstrates inhibition of amyloidogenesis (Morshedi et al. 2007).

Since ILs also interact with amino acid residues in proteins, it follows that ILs also affect amyloid stability. Some studies have investigated the suppression and promotion of amyloid formation using ILs (Table 2). As for ammonium-based ILs, tetramethylguanidium acetate ([TMG][Ac]) and EAN inhibited lysozyme amyloids, while propylammonium and butylammonium nitrates (PAN and BAN) and 2-methyloxyethylammonium nitrate (MEOAN) slightly promoted amyloid formation (Kalhor et al. 2009; Mangialardo et al. 2012). Triethylammonium-based ILs ([Tea][Y], Y=anion) with $H_2PO_4^-$ and HSO_4^- anions promote Aβ16-22 amyloid aggregation (Debeljuh et al. 2011a), and triethylammonium mesylate ([Tea][Ms]) suppresses amyloid formation of Aβ16-22 and Aβ1-40 peptides (Debeljuh et al. 2011a, b). Conversely, imidazolium- and pyridinium-based ILs promote amyloid formation (Bae et al. 2011), and the promotion of α-lactalbumin amyloid by [bmim][BF_4] was observed in other proteins (Hwang et al. 2009).

Importantly, investigating the potential use of ILs for suppression of amyloid formation involves elucidation of the mechanisms thereof. It has been suggested that the suppression or promotion of amyloid formation by ILs depends on the specific IL and on the nanostructure of the IL itself (Debeljuh et al. 2011a). Recently, ILs exhibited strong suppression of

Table 2 Amyloid forming ability of ionic liquids

Proteins	Effect of amyloid formation	Methods	References
Amyloid β (16-22) (Aβ16-22)	[Tea][HSO_4] ~ [Tea][H_2PO_4] > [Tea][Tfac] > [Tea][La] > [Tea][Tf] > [Tea][Ms]	ThT, TEM, and CD	Debeljuh et al. 2011a
Amyloid β (1-40) (Aβ1-40)	[Tea][Ms]: suppression	TEM and CD	Debeljuh et al. 2011b
α-Lactalbmin	[bmim][BF_4] > [bmim][PF_6] > [bmim][TFSI] > [bmim][CH_3SO_4]	ThT and TEM	Bae et al. 2011
α-Synuclein	[bmim][TFSI] > [bmim][BF_4]	ThT and TEM	Bae et al. 2010
	[bmim][TFSI] > [emim][TFSI] > [hmim][TFSI] > [Bzmim][TFSI] > [eDmim][TFSI] > [omim][FSI]	ThT and TEM	Hwang et al. 2009
	[bpyr][BF_4] > [omim][FSI] ~ [Phemim][FSI] ~ [bDmim][BF_4] ~ [bmim][BF_4] ~ [bmim][PF_6]	ThT and TEM	Hwang et al. 2009
Trypsin	[bmim][BF_4]: promotion	ThT and TEM	Bae et al. 2011
Insulin	[bmim][SCN] > PAN ~ EAN	FTIR and CR	Takekiyo et al. 2016
	[bmim][BF_4]: promotion	ThT and TEM	Bae et al. 2011
Lysozyme	EAN and [Tea][Ms]: suppression	SEM, CD, and CR	Byrne and Angell 2009
	PAN ~ BAN > MEOAN	ThT, TEM. CD, and ANS	Kalhor et al. 2009
	[TMG][Ac]: suppression	Raman	Mangialardo et al. 2012
	[bmim][BF_4]: promotion	ThT and TEM	Bae et al. 2011

insulin amyloid formation (Fig. 1a), and this suppression was due to the insulin–IL interactions (Fig. 1b) (Takekiyo et al. 2016). Moreover, the insulin–IL interaction and nano-heterogeneity structure of the aqueous IL solution protect the amyloid formation by heating.

As per the results of the insulin amyloid suppression, ILs tend to interact with the amino acid residues through electrostatic and hydrophobic interactions, and the interaction sites of ILs with amino acid residues are dependent upon the specific cationic and anionic species of IL (e.g., Fig. 1b). Therefore, IL nanostructure and the affinity between the ILs and specific amino acid residues both play important roles in the selection of ILs for their suppression and promotion effects on amyloid formation.

Ionic liquid-induced dissolution of amyloid aggregates

Some small compounds such as DMSO and guanidine hydrochloride have been previously used to dissolve amyloid aggregates (Table 3). Since ILs have the ability to dissolve cellulose (Hauru et al. 2012), which has a H-bonding structure similar to that of amyloid aggregates, this ability may be related to the advantage of the reconstruction technique of amyloid aggregates. However, there are few studies reporting the dissolution of amyloid aggregates using IL; one such study reports that ammonium-based ILs such as EAN demonstrated the ability to dissolve lysozyme amyloid (Byrne and Angell 2009).

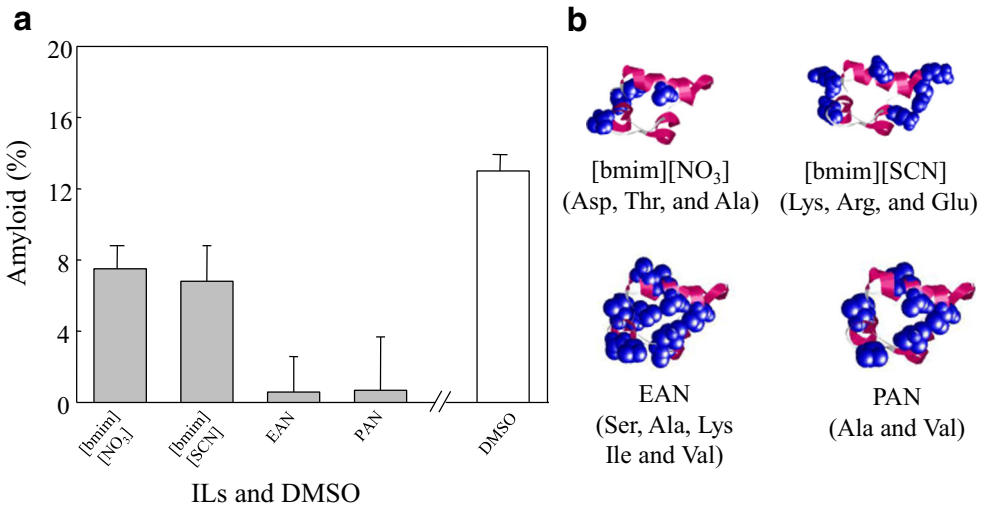

Fig. 1 **a** Insulin amyloid contents in aqueous solution with ILs (gray bars) and DMSO (white bar) with $x = 20$ mol%IL determined by FTIR spectra. **b** Interaction sites of ILs with insulin. The figure was reproduced from Takekiyo et al. (2016)

Table 3 Representative dissolution agent for various amyloids

Protein	Dissolution agent	Methods	References
β-Microglobulin	Guanidine hydrochloride	CD, ThT, and fluorescence	Narimoto et al. 2004
	Dimethyl sulfoxide (DMSO), Hexafluoroisopropanol and 2,2,2-Trifluoroethanol (TFE)	CD, light scattering, fluorescence, and EM	Hirota-Nakaoka et al. 2003
Insulin	DMSO	ThT, AFM, DLS, and FTIR	Loksztejn and Dzwolak 2009
	Guanidine thiocyanate	FTIR and TEM	Shammas et al. 2011
Amyloid β (25-35) (Aβ25-35)	DMSO	NMR, AFM, and UV-Vis	Ippel et al. 2002
Transthyretin (10-19)	TFE	CD and EM	MacPhee and Dobson 2000

To further evaluate the amyloid-dissolving ability of ILs, preliminary, we have investigated the dissolution of insulin amyloid aggregates in aqueous solutions with four ILs and DMSO ($x = 20$ mol%IL or DMSO) using FTIR spectroscopy (Takekiyo et al. unpublished data). Studied ILs were able to dissolve insulin amyloid, and the dissolved amyloid formed an α-helical structure (Fig. 2a). The dissolution ability rank order of ILs for insulin amyloid was [bmim][NO_3] ≥ [bmim][SCN] ≥ DMSO = PAN ≥ EAN; this dissolution ability was more strongly dependent on the cationic species of the IL than the anionic species. Imidazolium-based ILs demonstrated a stronger dissolving ability than DMSO and ammonium-based ILs. As mentioned previously, the amyloid-dissolving ability of DMSO is due to its basicity (Hirota-Nakaoka et al. 2003). Differences in dissolution abilities between ILs and DMSO appear to depend upon the basicity of the liquid. It is worth noting that the ability of ILs to dissolve cellulose is dependent upon the H-bonding basicity in the Kamlet-Taft (KT) parameters, a set of factors reflecting the solvent properties, measuring overall polarity

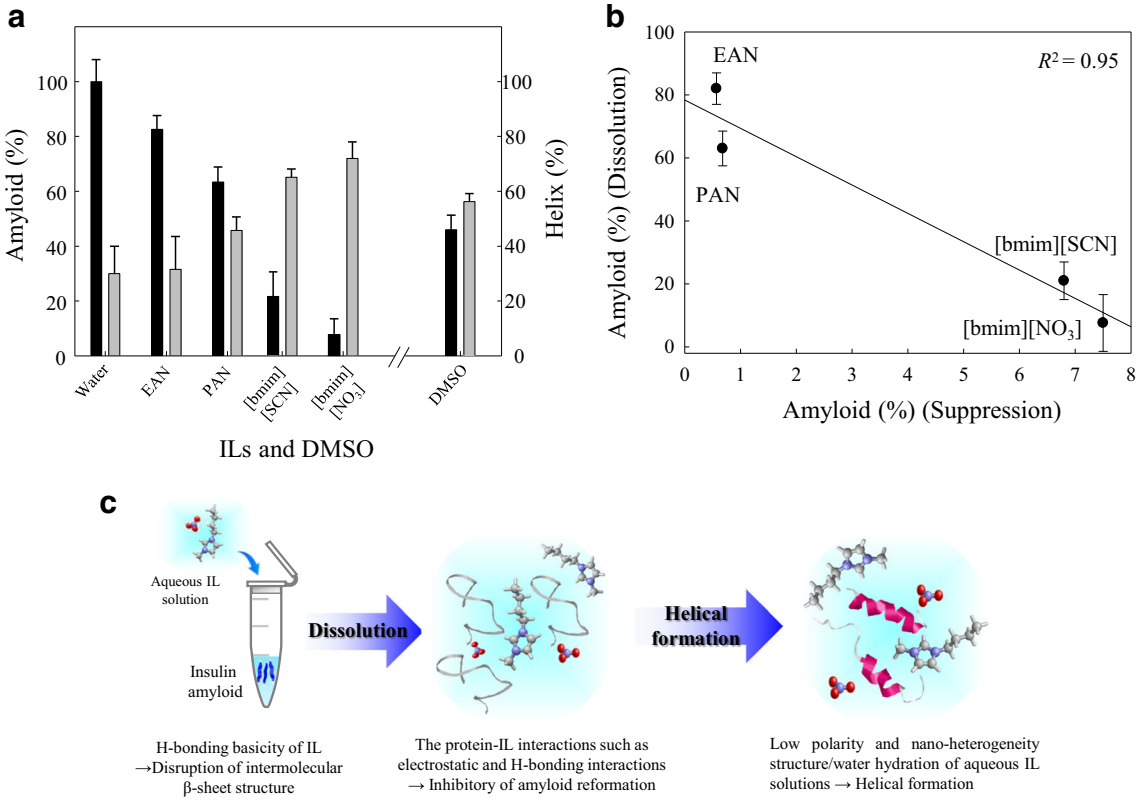

Fig. 2 **a** Amyloid (black bars) and helix (gray bars) contents of dissolved insulin amyloids in the aqueous solutions with ILs and DMSO with $x =$ 20 mol%IL determined by FTIR spectra. **b** Amyloid contents of the dissolution and suppression of insulin amyloid by the addition of ILs at $x = 20$. The correlation coefficients (R^2) determined by the least-squares analysis. **c** Scheme of dissolution mechanism of insulin amyloid by the addition of aqueous IL solutions at $x = 20$

by separately considering the H-bond acidity (α), H-bond basicity (β), and polarizability (π*) of the solvent (Hauru et al. 2012). Comparing the β-value in KT parameters of pure DMSO and ILs, the β-value of DMSO is 0.76 (Kamlet et al. 1983), while the β-values of studied imidazolium-based ILs range from 0.66 to 0.95 (Lungwitz et al. 2010). The β-values of imidazolium-based ILs are almost the same or slightly higher than DMSO, and those of EAN (β = 0.46) and PAN (β = 0.52) (Greaves and Drummond 2008) are lower than DMSO. The difference in the dissolution ability of ILs and DMSO for insulin amyloid may correlate with the H-bonding basicity (β-value).

The relationship between the suppression/dissolution abilities of ILs for insulin amyloid is intriguing. Remarkably, ILs with low suppression ability showed high dissolution ability (Fig. 2b). Entirely, imidazolium-based ILs have good suppression/dissolution abilities for insulin amyloid when compared to ammonium-based ILs.

Finally, we propose the dissolution mechanism of insulin amyloid in aqueous IL solutions (x = 20 mol%IL) (Fig. 2c). The addition of aqueous IL solutions to insulin amyloid induced the disruption of intermolecular H-bonding by the H-bonding basicity of ILs, and the dissolved insulin–IL interactions such as electrostatic interaction and H-bonding suppressed amyloid reformation (Takekiyo et al. 2016). Moreover, since the low polarity and nano-heterogeneity structure/water hydration of aqueous IL solutions enhance the intramolecular H-bonding in proteins (Takekiyo et al. 2013, 2017a), dissolved insulin in aqueous IL solutions forms a helical structure. However, although ILs have the ability to dissolve amyloid aggregates from insulin and lysozyme (Byrne and Angell 2009), detailed information for other amyloids is still unclear. It is well-known that the β-sheet structures constructing amyloid aggregates may be either parallel or antiparallel structures (Zou et al. 2013). Therefore, the differences in the amyloid structure may result in different dissolution abilities when different ILs are used. Further systematic investigation of how various amyloid aggregates are affected by ILs will allow further understanding of how ILs may be used to dissolve amyloid aggregates.

Conclusions and perspectives

In this review, we summarized the potential use of ILs for the suppression/dissolution agents of amyloid aggregates. The protein–IL affinity, such as protein–IL interactions (contribution to inhibitory of protein aggregation), and low polarity and nano-heterogeneity structure/water hydration (contribution to helical formation), was found to be the primary biochemical basis for the suppression of amyloid formation. The H-bonding basicity of ILs plays a role in the dissolution ability for insulin amyloids. In addition to these factors, IL solutions easily form a glassy state, which facilitates the cryopreservation of biomolecules at 77 K (Yoshimura et al. 2011). Related to this, ILs are already known for their potential use in cryopreservation/refolding of

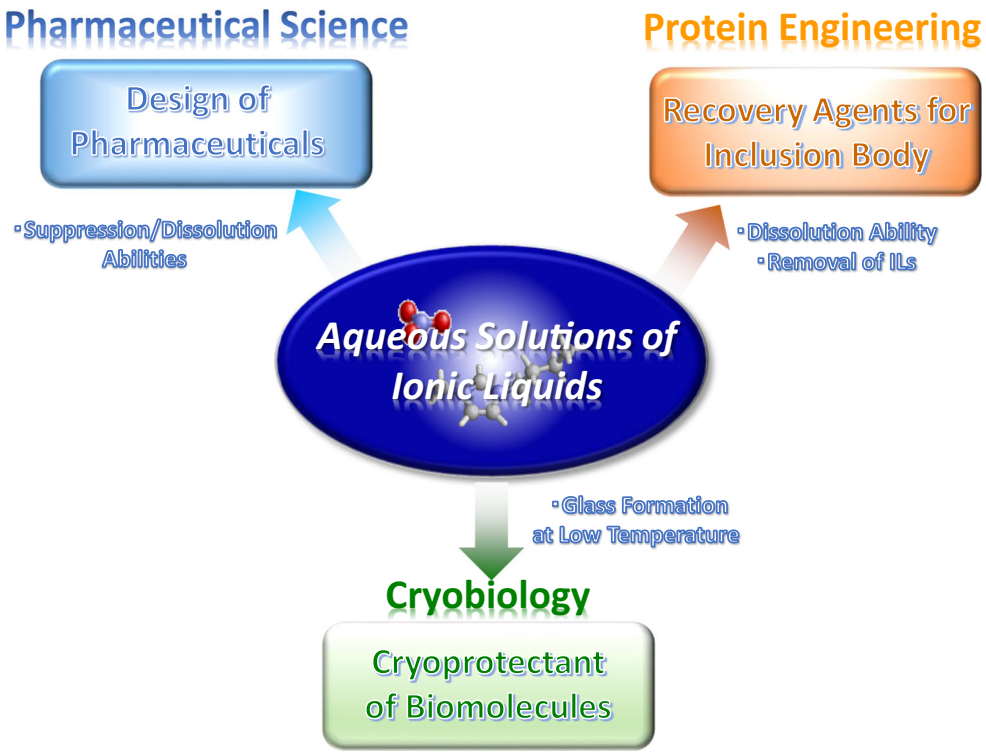

Fig. 3 Advantages of ILs for potential application in biological engineering and pharmaceutical sciences

proteins (Yoshimura et al. 2016; Takekiyo et al. 2017b). Some techniques for removing IL from aqueous protein solutions, such as column chromatography and dialysis, have been reported (Fujita et al. 2016; Takekiyo et al. 2017b). Our understanding of long-term preservation agents that also dissolve aggregated proteins stems from the import and export of valuable proteins, and the challenges of reduced protein function resulting from the preparation of large-scale stock solutions. Aqueous IL solutions may therefore have the potential to increase the suppression/dissolution of amyloid aggregates and also to improve the cryopreservation of dissolved proteins.

Finally, the toxicity of ILs toward biological systems, such as biomolecules and cells, is under intense study (Pham et al. 2010; Kudlak et al. 2015). The toxicity of ILs appears to be dependent on the constructing ions and target biological system. Together with the development of nontoxic ILs for use with protein systems, the basic information of suppression/dissolution/cryopreservation abilities of ILs for target proteins will yield great potential for additional developments in pharmaceutical science, cryobiology, and protein engineering (Fig. 3).

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Compliance with ethical standards

Conflict of interest Takahiro Takekiyo declares that he has no conflict of interest. Yukihiro Yoshimura declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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