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Curcumin modulates the self-assembly of the islet amyloid polypeptide by disassembling α-helix

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ABSTRACT

Understanding how small molecules affect amyloid formation is of major biomedical and pharmaceutical importance due to the association of amyloid with incurable diseases including Alzheimer's, Parkinson's, and type II diabetes. Using solution state ^{1}H NMR, we demonstrate that curcumin, a planar biphenolic compound found in the Indian spice turmeric, delays the self-assembly of islet amyloid polypeptide to NMR-invisible assemblies. Accompanying circular dichroism studies show that curcumin disassembles α-helix in maturing assemblies of IAPP. The amount of α-helix disassembled correlates with predicted and experimentally determined helical content of IAPP obtained by others. Taken together, these results indicate that curcumin modulates IAPP self-assembly by unfolding α-helix on pathway to amyloid. The implications of this work in the elucidation of the mechanism for amyloid formation by IAPP in the presence of curcumin are discussed.

1. Introduction

The self-assembly of intrinsically disordered proteins to form highly ordered amyloid fibrils possessing the cross β-sheet structure [1] is associated with progressive, typically late-onset diseases including Alzheimer's, Parkinson's, and type 2 diabetes (T2D) [2]. Collectively, these diseases are known as amyloidoses characterized by the presence of amyloid deposits in the diseased organs [3]. T2D is the most common metabolic disease worldwide. According to the World Health Organization, there are ca. 200 million people with the disease. Diabetes is a leading cause of retinopathy, renal disease, neuropathy, and lower limb amputations and is a major risk factor for stroke and cardiovascular disorders [4].

The self-assembly of the islet amyloid polypeptide (IAPP) (a.k.a. amylin) (Fig. 1A), a hormone made up of 37 amino acid residues that is co-secreted with insulin by the pancreatic β cells, appears to contribute an essential role in β-cell death in T2D [5,6]. A serine-to-glycine substitution at position 20 of IAPP leads to early-onset T2D in Asian patients [7] and to increased propensity of IAPP to self-assemble [8]. The amyloid cascade hypothesis, initially formulated for the role of amyloid formed by the amyloid-β protein (Aβ) in Alzheimer's disease [9], proposes that assemblies of IAPP initiate a process that leads to β-cell death and dysfunction. The proximate cytotoxic species appear to be much smaller than the mature fibrils [5]. For example, oligomers of IAPP permeabilize membranes [10–12] leading to unregulated flux of cell ions and molecules [13]. Interestingly, an antibody that binds to toxic oligomers of Aβ also recognizes toxic oligomers from other amyloidogenic proteins including IAPP, suggesting that the oligomers share common structural features [14,15].

If the amyloid or oligomer cascade hypothesis is proven to play an essential role in the pathogenesis of T2D, then an attractive strategy for therapeutics is modulation or inhibition of IAPP self-assembly. A small molecule that has been shown to accomplish this is curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (Fig. 1B), a planar biphenolic yellow pigment found in turmeric (Curcuma longa), widely used for centuries as spice and food coloring agent and possessing anti-inflammatory, antioxidant, antiviral, and chemo-preventative properties as reviewed recently [16]. Daval et al. showed that curcumin reduces IAPP fibril formation and that the assemblies formed show a different morphology and structure [17]. The effects of curcumin on the self-assembly of Aβ have also been studied. Necula et al. demonstrated that curcumin inhibits the oligomerization but not the fibrillization of Aβ42 [18]. Working backwards, i.e., starting with fibrils, Yang et al. [19] showed that curcumin disassembles fibrils of Aβ40. However, the mechanism for the ability of curcumin to inhibit oligomerization or modulate fibrillization and disassemble large assemblies has not been reported. This mechanism is important for the basic science of protein self-assembly and for the design of other anti-amyloid molecules with better pharmacological properties and increased inhibition potency.

We have, in the current study, investigated the effects of curcumin on the self-assembly of IAPP using solution-state ^{1}H nuclear magnetic resonance (NMR) and circular dichroism (CD) to obtain

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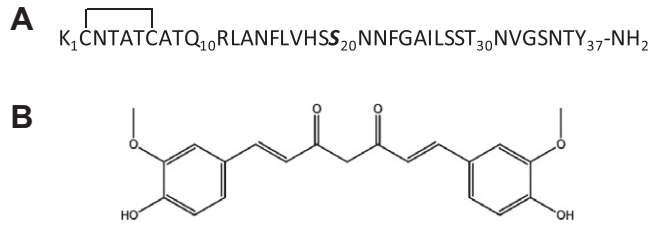

Fig. 1. (A) Primary structure of human IAPP. The residues Cys2 and Cys7 are joined by a disulfide bond. The N- and C-termini are free and amidated, respectively. In some cases of early-onset T2D, Ser 20 is replaced by glycine. (B) The chemical structure of curcumin (a.k.a. diferuloylmethane). The molecule has two substituted aromatic groups joined by a rigid, planar, seven-carbon linker.

kinetic and structural data, respectively. Curcumin significantly lengthened the lag time of self-assembly. CD of maturing assemblies in the presence of curcumin showed disassembly of α-helix. We discuss here mechanistic insights into IAPP self-assembly in the absence and presence of curcumin thus obtained.

2. Materials and methods

2.1. Sources of IAPP

IAPP was purchased from NEO Peptide. IAPP-S20G was made in house using an Applied Biosystems 433A peptide synthesizer (Life Technologies Corp.) and standard 9-fluorenylmethoxycarbonyl chemistry. To minimize aggregation during synthesis, pseudoproline dipeptide derivatives were used at the Ala8-Thr9 and Leu27-Ser28 locations [20]. After synthesis, the resin was sent to Biomer Technologies for cleavage, disulfide bond formation, and purification. The success of the production of IAPP-S20G was determined by mass spectrometry.

2.2. Preparation of stock solutions of IAPP and curcumin

A stock solution of IAPP was prepared by dissolving the polypeptide in ice-cold 10 mM NaH_2PO_4 buffer (pH 4.3). To remove undissolved peptide and large aggregates, the samples were centrifuged at 16000*g* for 30 s, followed by careful transfer of the supernatant into clean tubes. The concentration of IAPP in the final supernatant was determined by UV absorbance at 214 nm as described elsewhere [21].

Curcumin (Acros Organics) was dissolved in ethanol (identified here as the vehicle) and its concentration, determined by UV–Vis using a molar extinction coefficient of $\varepsilon_{429} = 55000\ M^{-1}\ cm^{-1}$, [22] was determined to be 9.3 mM.

2.3. CD spectroscopy of IAPP assemblies

All CD spectra were acquired at 25 °C using a JASCO J-815 spectropolarimeter. Stoppered quartz cuvettes with a path length of 1 mm were used. Spectra were acquired from 260 to 195 nm at intervals of 1 nm with an averaging time of 4 s. All samples were kept at 25 °C in between acquisition of spectra. To minimize sample perturbation, the samples were incubated in the CD cuvettes.

2.4. Transmission electron microscopy (TEM) of IAPP assemblies

Seven microliters of the NMR or CD samples were placed on a carbon-coated copper grid and incubated for two minutes and then stained with 1% aqueous uranyl acetate solution. Images of the samples were recorded at the Core Electron Microscopy Facility of the University of Massachusetts Medical School.

2.5. NMR spectroscopy of IAPP assemblies

Aliquots of ice-cold IAPP and curcumin stock solutions needed to prepare 600 μl of sample containing the desired curcumin to IAPP ratio (mole/mole) were mixed in an Eppendorf tube and carefully transferred into an NMR tube immersed in ice. Two micro liters of sodium azide solution (concentration ~ 1 mg/ml) were added to the sample. The tube was then loaded into the NMR probe pre-cooled to 4 °C. One-dimensional (1D) ^{1}H NMR spectra were then recorded using a 600 MHz Varian INOVA spectrometer. Water suppression was accomplished by presaturation. All spectra were acquired with a relaxation delay of 2 s and 1400 scans and were processed with line broadening of 0.3 Hz. Chemical shifts are reported relative to the methyl resonance of 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) at 0 ppm. Samples were stored at 4 °C in between acquisition of spectra.

The peak area of the methyl peak of DSS which does not change with time was arbitrarily assigned a value of 1. The normalized peak area in the backbone NH region (7.9–9.0 ppm) was then determined. The remaining normalized peak area at a particular timepoint was calculated using the following equation:

$$\text{remaining peak area } (\%) = \frac{\text{normalized peak area at day x}}{\text{normalized peak area at day 0}} \times 100$$

3. Results and discussion

3.1. Curcumin delays the self-assembly of IAPP to NMR-invisible assemblies

We first addressed the question: does curcumin affect the kinetics of self-assembly by IAPP? A widely used method for kinetic studies of amyloid formation is thioflavin T (ThT) fluorescence [23]. However, recent work by Daval and coworkers [17] showed that curcumin directly interferers with ThT fluorescence presumably by competing against ThT for the same binding site. An alternative method is nuclear magnetic resonance spectroscopy (NMR), previously used by us and others in monitoring IAPP self-assembly [21,24]. The biophysical basis of using NMR is simple: signal intensities of monomers decrease with time as a result of self-assembly to NMR-invisible assemblies, i.e., species whose peaks are broadened beyond detection because of their large size and thus long rotational correlation times [21,25]. To monitor the self-assembly of IAPP in the absence and presence of curcumin, we acquired one-dimensional ^{1}H NMR spectra of IAPP only and IAPP + curcumin over a span of more than 40 days at 4 °C. We monitored the self-assembly at a temperature much lower than room temperature (~25 °C) to possibly detect new peaks that would indicate the presence of NMR-visible intermediates. Fig. 2 presents the amide and aromatic regions of spectra acquired immediately after sample preparation (day 0) and after 20 and 45 days of incubation. From a qualitative analysis of all spectra recorded, we observed that the peak intensities in the backbone amide, side chain amide, and aromatic regions of monomers in each sample decreased uniformly. No new peaks appeared in all spectra obtained. Together, these results are consistent with a one-step pathway of IAPP self-assembly based on NMR, i.e., loss of NMR-visible monomers to NMR-invisible assemblies [21].

We then determined the remaining peak area in the amide regions of the ^{1}H NMR spectra in Fig. 2 using Eq. 1. The aromatic region was not included in this analysis because the signals from the aromatic protons of curcumin are also found in this region. After 45 days of incubation, 76% of the amide signals in the sample with curcumin remain. On the other hand, only 41% of the amide signals remain in the sample without curcumin. Together, these results

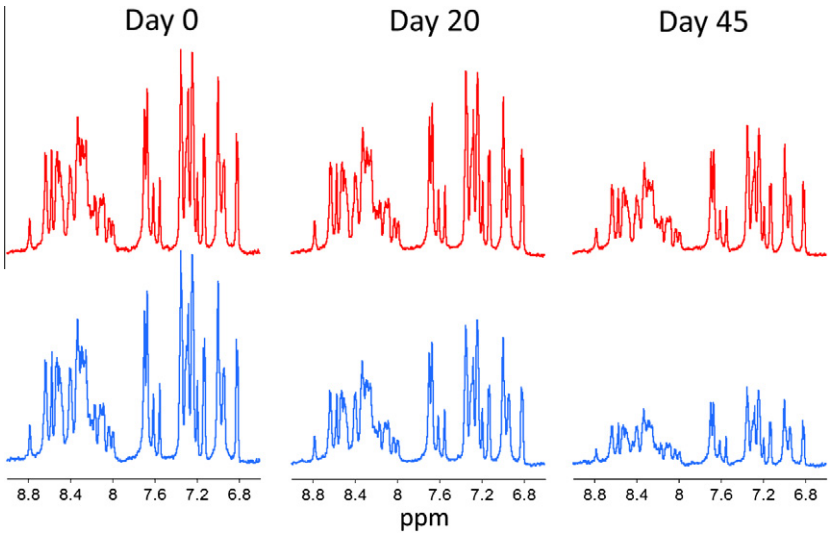

Fig. 2. Curcumin delays the self-assembly of IAPP to NMR-invisible assemblies. Portions of 1D ^{1}H NMR spectra of IAPP in the presence (red) and absence (blue) of curcumin. As self-assembly occurs, the intensities of the peaks in the amide and aromatic regions decrease. After 45 days of incubation, 41 and 76% of the starting amide and aromatic signals in the samples without curcumin and with curcumin, respectively, remain. Both samples contain 44 μM IAPP in 10 mM NaH_2PO_4 buffer (pH 4.3). The peaks due to the aromatic protons of curcumin overlap with those of the aromatic protons of IAPP (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

indicate that curcumin delays the self-assembly of IAPP to NMR-invisible assemblies.

Transmission electron microscopy (TEM) showed the presence of fibrils in both samples after ~45 days of incubation (Supplementary Fig. S1) and differences in morphology were observed. Mature fibrils that are indeterminately long are formed by IAPP in the absence of curcumin. Immature fibrils that are much shorter are formed in the presence of curcumin, consistent with the NMR results indicating that curcumin delays the self-assembly of IAPP.

3.2. IAPP self-assembles via an α-helical intermediate

In order to determine the structure present in the NMR-invisible assemblies, we performed complementary circular dichroism studies of the self-assembly of IAPP. For control (vide infra), we also included IAPP−S20G which contains the serine-to-glycine substitution at position 20 associated with early-onset T2D [7] and increased amyloidogenicity [8,26]. CD spectra of IAPP and IAPP-S20G acquired at 25 °C over a period of 5 days show that both self-assemble via an α-helical intermediate (Supplementary Fig. S2A and S2B) as indicated by spectra possessing a minimum at 208 nm corresponding to the $\pi \rightarrow \pi_{||}^*$ transition of the amide groups of the α-helix [27]. In spectra of pure α-helices, the minimum at 208 nm is accompanied by another one at 222 nm corresponding to the $n \rightarrow \pi_*$ transition of the amide groups [27]. In samples that contain significant amounts of α-helix and β-sheet, however, the minimum at 222 nm is obscured by the minimum at 217–218 nm representing the $n \rightarrow \pi_*$ transition of β-sheets [28]. After 5 days of incubation, the negative part of the dichroic spectrum of IAPP-S20G is symmetric with a minimum at 217 nm, typical of β-sheets (Supplementary Fig. S2B). TEM of the sample shows the presence of mature assemblies, i.e., fibrils that are indeterminately long, smooth and with a uniform diameter of ca. 12 nm (inset, Supplementary Fig. S2B). In contrast, the negative part of the dichroic spectrum of IAPP is asymmetric and contains a discontinuity near 207 nm, suggesting the presence of α-helix and β-sheet (Supplementary Fig. S2A). TEM of the sample shows the dominant presence of short and rough fibrils, typical of immature assemblies that contain some α-helix [21,29] (inset, Supplementary Fig. S2A). Because of the absence of a suitable reference database for amyloid assemblies [21], we did not deconvolute the CD spectra for determination of secondary structure distribution.

Together, our CD and TEM results suggest that the α-helix persists longer in IAPP than in IAPP-S20G. This conclusion is consistent with our recent work using IAPP(11-25) fragments which contain the part of IAPP that may be involved in the initial intermolecular interactions required for self-assembly [21]. In particular, we showed that IAPP(11-25)-S20G undergoes an α-helix to β-sheet conformational rearrangement to form mature fibrils similar to those shown in Supplementary Fig. S2B. This conversion is slowed in IAPP(11-25), however, and as a result yielded a spectrum similar to α-helical assemblies [21].

3.3. Curcumin disassembles the α-helix in maturing assemblies of IAPP

We then determined the susceptibility of the α-helix in the growing assemblies of IAPP to disassembly. To do so, we added curcumin to samples similar to the day-5 CD samples shown in Supplementary Fig. S2A and then continued the acquisition of dichroic spectra on a daily basis for an additional 14 days. Fig. 3A presents spectra acquired up to 8 days after the addition of curcumin at a ratio of 1:1 (mole curcumin: mole polypeptide) to IAPP. This ratio is based on previous work by others showing that curcumin binds to α-helical intermediates in amyloid formation at a 1:1 ratio (mole:mole) [30]. We noted that the spectra possess an isodichroic point at 203 nm, indicative of a two-state transition from α-helix to random coil [28,31–33]. This transition is also indicated by the loss of negative dichroism at 222 and 208 nm and of positive dichroism at 195 nm (Fig. 3A). The absolute magnitudes of the changes in ellipticity ($\Delta\theta$) follow the order $\Delta\theta_{195\ nm} > \Delta\theta_{208\ nm} > \Delta\theta_{222\ nm}$, consistent with the relative rotational strengths (i.e., integrated intensities) of the α-helix at the three wavelengths [27]. Taking together these observations, we conclude that curcumin disassembles the α-helix present in the maturing assemblies of IAPP to random coil. This effect of curcumin is consistent with previous work by others showing that binding of the small molecule to the predominantly α-helical human serum albumin leads to partial protein unfolding, i.e., the α-helix content was reduced while random coil and turn increased [34].

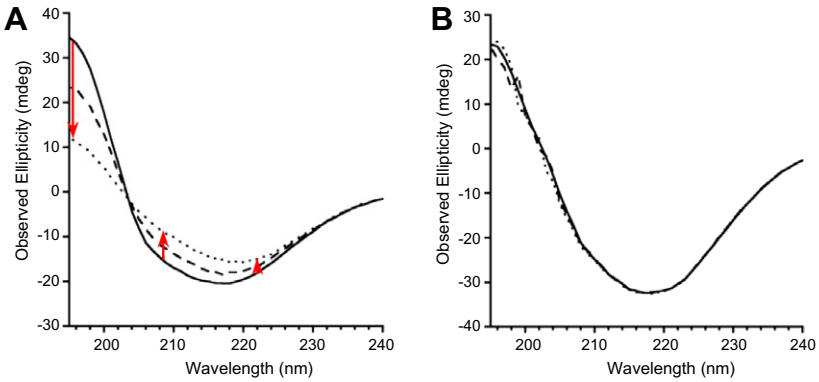

Fig. 3. Curcumin unfolds α-helices but does not affect β-sheets. (A) Circular dichroic spectra of assemblies of IAPP in the presence of curcumin acquired at day 0 (solid line), day 1 (broken line), and day 8 (dotted line). In the presence of curcumin, the α-helix is unfolded to random coil. The arrows pointing up indicate the loss of negative ellipticity while the arrow pointing down indicates the loss of positive ellipticity. (B) Circular dichroic spectra of assemblies of IAPP-S20G in the presence of curcumin acquired at day 0 (solid line), day 8 (broken line) and day 14 (dotted line). The β-sheet content of the assemblies is not affected by curcumin. In (A) and (B), the IAPP concentrations are 59.5 and 91.3 μM, respectively. Curcumin is present in a 1:1 ratio (mole IAPP/mole curcumin). Both samples were prepared in 10 mM NaH_2PO_4 buffer (pH 4.3).

As control, we also incubated day-5 IAPP assemblies in the presence of the same amount of ethanol used in the curcumin-containing samples (1–2 μL). The CD spectrum obtained after 14 days of incubation with ethanol was essentially identical to the spectrum acquired before the addition of the alcohol (Supplementary Fig. S3), demonstrating that the effect observed in Fig. 3A is due to curcumin.

The other secondary structure present in the assemblies of IAPP that could be disassembled by curcumin is β-sheet. After 8 days of incubation with curcumin, the spectrum of IAPP has a single minimum at 220 nm consistent with β-sheet (Fig. 3A). Additional spectra acquired from day 9 to day 14 are essentially identical to the day-8 spectrum (data not shown). We also added curcumin to the β-sheet assemblies formed by IAPP-S20G and observed no significant changes in the CD spectra recorded up to 14 days of incubation (Fig. 3B). Taken together, these results suggest that curcumin does not disassemble β-sheet assemblies of IAPP and IAPP-S20G.

To estimate the amount of α-helix unfolded in IAPP, we determined the loss in the rotational strength from 204 to 240 nm in the day-8 spectrum relative to the day-0 spectrum (Fig. 3A). To do so, the areas under the *x*-axis of the 2 spectra were calculated using the trapezoidal rule. The loss in rotational strength in the day-8 spectrum is ca. 20%. Interestingly, the 20% loss is in good agreement with the number of residues in the region of IAPP predicted to have the highest α-helix propensity, i.e., residues 10–17 or 22% of the polypeptide [35]. Electron spin and nuclear magnetic resonance studies of IAPP in the presence of helix-stabilizing membranes support this prediction [35,36].

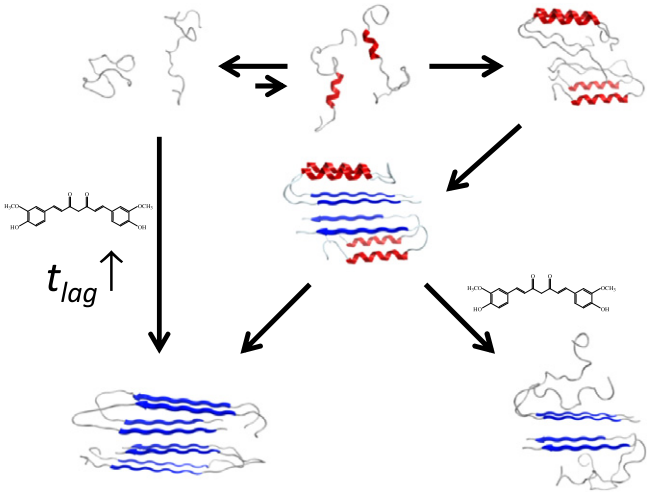

Fig. 4. Schematic representation of the self-assembly of IAPP. In the absence of curcumin, parts of the N-terminus of monomeric IAPP transiently sample the α-helical conformational space as indicated by the black double arrows. The helices come together to form a helical oligomeric intermediate (upper right) bringing the β residues found in the C-terminus in close proximity for the formation of intermolecular β-sheets. The α-helix in the intermediate in the center of the figure is disassembled by curcumin. In the absence of curcumin, it is converted to β-sheet. When self-assembly begins in the presence of curcumin, the helical intermediate is not formed but fibrils still form presumably via another intermediate that requires a longer lag time.

3.4. Mechanistic implications

Overall, our results argue that the α-helix in the growing amyloid assemblies of IAPP is exposed and not buried in the inaccessible amyloid core. There is precedence for an exposed α-helix in amyloid assemblies. Sivanamdam et al. showed that the rigid and dehydrated amyloid core of the huntingtin amyloid fibril is decorated with exposed and mobile N-terminal residues in the α-helix conformation [29]. The existence of an exposed N-terminal α-helix is significant for IAPP self-assembly to amyloid fibrils. A schematic for the conversion of predominantly disordered IAPP to highly ordered amyloid fibrils is presented in Fig. 4. IAPP forms transient α-helices as indicated by analysis of secondary chemical shifts [37,38]. As previously hypothesized by others and us, these transient α-helices come together to form NMR-invisible helical oligomers stabilized by helix–helix contacts [10,21,35,39]. By doing so, the entropic cost of oligomer formation is lowered and the C-terminus which contains the part of IAPP that has the highest propensity to form β structure is positioned close to other C-termini thereby facilitating the formation of intermolecular β-sheets. Because the helices remain exposed during this process, they are susceptible to disassembly by curcumin. A mechanism for helix disassembly is binding of curcumin to the individual helices in a manner that the formation of the stabilizing helix–helix interactions is prevented. This mechanism is supported by work of others showing affinity of curcumin for α-helix containing targets. For example, binding of curcumin to the α-helical intermediate in prion self-assembly inhibited the accumulation of the scrapie form of the protein [30]. Complexation of curcumin with human serum albumin led to an increase in random coil and turn structures at the expense of α-helix [34].

In the presence of curcumin, the time required for the conversion of IAPP monomer to NMR-invisible assemblies including

β-sheet is increased significantly, suggesting that curcumin inhibits the formation of the helical oligomers that are on-pathway to amyloid. Curcumin however does not inhibit fibrillization (Supplementary Fig. S1). Together, these results suggest that more than one pathway leads to fibril formation. Finally, the correlation of assembly structure and cytotoxicity has not been established for IAPP. However, this work suggests that if the helical assemblies are the proximate toxic species, then curcumin, shown here to disassemble α-helix, is an attractive therapeutic.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.05.013.

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