Cotranslational Folding of Globin*

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Globin synthesis in a wheat germ cell-free translation system was performed in the presence of [3H]hemin and [35S]methionine to determine the minimal length of the nascent ribosome-bound globin chain capable of heme binding. Nascent polypeptides of predetermined size were synthesized on ribosomes by translation of truncated mRNA molecules. Analysis with the use of sucrose gradient centrifugation and puromycin reaction revealed that the ribosome-bound N-terminal α-globin fragments of 140, 100, and 86 amino acid residues are capable of an efficient heme binding, whereas those of 75, 65, and 34 amino acid residues display a significantly weaker, or just nonspecific, affinity to heme. This indicates that the ribosome-bound nascent chain of 86 amino acid residues has already acquired a spatial structure that allows its interaction with the heme group or that heme attachment promotes the formation of the proper tertiary structure in the ribosome-bound nascent polypeptide. In any case the cotranslational folding of globin is suggested.

The mechanism by which the growing polypeptide chain acquires its native conformation has been discussed in many recent reviews (1–5). Historically, most protein-folding studies were based on the analysis of protein refolding in vitro. These studies have provided basic insights into the principles and mechanisms governing the folding of polypeptides into compact three-dimensional structures (6–9). However, the in vivo folding is assumed to proceed cotranslationally (10–15). Evidence suggesting the cotranslational protein folding has come from experiments that demonstrated (i) the enzymatic activity of the growing polypeptide on the ribosome (16–21), (ii) the formation of correct epitopes able to bind corresponding conformational antibodies (22), and (iii) the formation of correct disulfide crossbridges in the growing nascent chains (23–28).

Previously we reported data indicating that heme attachment to the globin chains may proceed cotranslationally (29).

Analysis of globin synthesis in cell-free extracts of rabbit reticulocytes carried out in the presence of [3H]hemin revealed the presence of [3H]hemin in the polyribosome fraction synthesizing globin chains. The addition of puromycin resulted in the release of both [3H]hemin and [14C]-labeled leucine polypeptide from the polyribosomes. The data obtained indicated cotranslational heme binding to the nascent globin chains and thus to the cotranslational folding of the globin molecule since heme binding in the case of globin molecules is a function of the definite protein structure (30, 31). However, the possibility of globin tetramer assembly on the ribosome in those experiments could not be excluded. Cotranslational trimerization of the retrovirus cell attachment protein, ρ1, has been demonstrated recently (32), and thus the assembly of the nascent globin chains could as well be the case. If this was the case, the previously obtained data could be alternatively explained by the presence of complete globin chains (with labeled hemin) associated with the nascent chain.

To rule out this possibility, we have used the wheat germ cell-free translation system, which does not contain endogenous globin molecules. We have also performed the translation experiments with α-globin synthesis, which, in contrast to β-globin, does not form the tetramer structure (31). We have found that α-globin is capable of heme binding during its synthesis on the ribosome. In addition, we have demonstrated that incomplete α-globin molecules of 140, 100, and 86 amino acid residues (lengths are given excluding the first initiator methionine) are capable of cotranslational heme binding with an approximately equal efficiency, whereas polypeptide chains of 75, 65, and 34 amino acid residues display a significantly weaker, or just nonspecific, affinity to heme. This shows that the nascent chain of 86 amino acid residues possesses a spatial structure that allows its interaction with the heme group or that the heme attachment promotes the formation of the proper tertiary structure of the growing polypeptide on the ribosome. Hence, the cotranslational folding of globin molecule is suggested.

EXPERIMENTAL PROCEDURES

In Vitro Transcription of α-Globin cDNA—The plasmid PHST101 (rabbit α-globin subclone PSP64) containing α-globin cDNA under control of the SP6 promoter was the gift of Professor J. Ilan, Case Western Reserve University. The transcription reaction was carried out according to Gurevich et al. (33) in 500 µl (total volume) of 80 mM HEPES-KOH buffer, pH 7.5, containing 16 mM MgCl2, 2 mM spermidine, 20 mM dithiothreitol (DTT), 3 mM ATP, 3 mM GTP, 3 mM UTP, 15 µM (375 units) of RNasin (Pharmacia Biotech Inc.), 25 µg of BamHI-linearized DNA template, and 2000 units of SP6 RNA polymerase (Fermentas). The reaction was carried out at 37 °C for 2.5 h and stopped by phenol/chloroform extraction. The transcript was purified by LiCl precipitation and washed with 70% ethanol (34). An aqueous solution (3.44 mg/ml) of the transcript was used in translation experiments.

Cell-free Protein Synthesis—Cell-free translation of the α-globin mRNA was performed using wheat germ extract as described by Clemens (35). The reaction mixture contained 20 mM HEPES-KOH buffer, pH 7.5, 3 mM Mg(CH3COO)2, 100 mM KCH3COO, 2.5 mM DTT, 1.3 mM ATP, 0.25 mM GTP, 50 µM spermidine, 16 mM creatine phosphate, 40 µg/ml creatine phosphokinase. The concentration of mRNA was 100 µg/ml. The specific radioactivities of [35S]methionine and [3H]hemin used in the experiments were 1 and 1.2 mCi/ml, respectively. [3H]Hemin was prepared by the hot tritium bombardment technique (36) as described previously (29). The final reaction volume was 100 µl. The translation was carried out at 24 °C. After 25 min of incubation, the
reaction mixtures were subdivided into two equal portions. Puromycin was added to a final concentration of 1.5 mM to one of the portions, and the incubation of both portions was continued for an additional 10 min.

**RNase H Digestion of α-Globin mRNA**—To produce α-globin peptides of predetermined lengths in the cell-free system, the α-globin mRNA was digested with RNase H in the presence of corresponding antisense oligodeoxyribonucleotides before translation. The following 20-mer oligodeoxyribonucleotides were used to produce the truncated mRNA encoding for the N-terminal α-globin fragments with the lengths indicated as numbers of amino acid residues: α34, 5′-GTCTTGGTGTTGGGG-GAAGC-3′; α65, 5′-TGGCAGCGCGCTTTGTCAG-3′; α75, 5′-GACACGGGCGCAGCGCAG-3′; α86, 5′-ACCACCAGCTTCTGCCG-TG-3′; α100, 5′-ACCGACACGGCAGGACAG-3′; α140, 5′-TCGAGGCTCCAGCTAAGC-3′.

10 μg of full-sized globin mRNA was incubated at 37 °C with a 50-fold molar excess of a complementary 20-mer oligodeoxyribonucleotide and 100 units of RNase H from *Escherichia coli*. The reaction was carried out for 1 h in 40 mM Tris-HCl buffer, pH 7.6, containing 1 mM DTT, 1 mM MgCl₂, and 30 mg/ml bovine serum albumin. Truncated globin mRNAs obtained after digestion were used in the translation experiments (Fig. 1). Completeness of RNA digestion was controlled by electrophoresis as numbers of amino acid residues:

Full-length α-globin mRNA: 140 residues

- α86 mRNA: 86 residues
- α100 mRNA: 100 residues
- α140 mRNA: 140 residues

**RESULTS**

Full-length α-Globin Is Capable of Cotranslational Heme Binding.—It was shown earlier that globin molecules are capable of cotranslational binding of heme in a homologous rabbit reticulocyte cell-free system (29). Here we used the same methodology but with the wheat germ cell-free system. The question was whether the individual globin molecule (α- or β-chain) is capable of cotranslational heme binding. For the *in vitro* translation in a wheat germ system we chose the α-globin that has a 10-fold stronger ability to bind the heme group as compared with the β-globin (30, 39) and, in contrast to β-globin, does not form the tetramer structure (31).

Fig. 2 shows that [3H]hemin is detected in the ribosome fraction translating α-globin mRNA. The addition of puromycin results in the release of a major portion of both [3H]hemin and [35S]methionine, 50-μl aliquots of the translation mixture were washed before sucrose gradient centrifugation with 2 ml of 10 mM HEPES-KOH buffer, pH 7.6, 100 mM KCH₃COO, 10 mM Mg(CH₃COO)₂, 1 mM DTT, and 0.1 mM EDTA on the Centricon C30 (Amicon Inc.) microconcentrator (30 min, 2000 × g, 4 °C). After ultracentrifugation, 100-μl aliquots of the washed translation mixture were layered on the top of linear 0.5–1.5 m sucrose gradients in 10 mM HEPES-KOH buffer, pH 7.6, 100 mM KCH₃COO, 10 mM Mg(CH₃COO)₂, 1 mM DTT, and 0.1 mM EDTA. Centrifugation was done for 2.5 h at 41,000 rpm in a Beckman SW 41 rotor at 4 °C. The gradients were pumped from the bottom, and absorbance at 278 nm was continuously recorded. 400-μl fractions were collected, and the radioactivity was counted.

However, the question is whether the heme retention can be observed on incomplete nascent globin chains, especially after both histidine imidazole groups of the E and F helices can be observed on incomplete nascent globin chains, especially after both histidine imidazole groups of the E and F helices are necessary for heme attachment have emerged from the ribosome. Taking into account that the translating ribosome may protect about 15–40 amino acid residues of the nascent peptide (40–45), it could be assumed that only the nascent peptides of...
Incorporation of $^{35}$S-methionine and $^3$H-hemin into the wheat germ extract ribosome fraction during translation of truncated $\alpha$-globin mRNAs. Top panels, no antibiotic added; lower panels, puromycin was added before centrifugation. A, $\alpha$-globin 100; B, $\alpha$-globin 86; C, $\alpha$-globin 86 produced after SP6 transcription of the short $\alpha$-globin PCR fragment; D, $\alpha$-globin 75; E, $\alpha$-globin 65.
approximately 100 amino acid residues and longer were capable of binding the heme (29).

To answer this question, the method of translation arrest by antisense oligodeoxynucleotides was chosen. The translation of mRNAs, truncated by RNase H in the presence of complementary oligonucleotides, results in nascent polypeptides of predetermined lengths attached to the ribosome as was reported previously (46). It was also reported that the dominant RNase H cut occurs at the RNA 5′-end in the RNA oligodeoxyribonucleotide complex in conditions of complete hydrolysis (47). Thus, the length of nascent peptide is predictable (48, 49). We started with the globin mRNA lacking the last 3′-terminal coding triplet. Sucrose gradient centrifugation analysis revealed that such an incomplete nascent globin peptide (α-globin 140; the length here does not include the first initiator methionine) is capable of heme binding during translation in the wheat germ system (not shown). Using the same approach, we found that an incomplete globin peptide of 100 amino acid residues (α-globin 100) is also capable of cotranslational heme binding (Fig. 3A). Surprisingly, the same has been demonstrated for a shorter globin peptide of 86 amino acid residues lacking the heme-binding histidine residue at position 87 (Fig. 3B). Determination of the 3′-end and sequencing of the α86 mRNA showed slight heterogeneity of the α86 mRNA 3′-end (not shown). To prove that an α-globin peptide of 86 amino acid residues is capable of heme binding, we performed the experiments with α86 mRNA obtained after SP6 transcription of a PCR-generated template containing SP6 promoter and the corresponding part of the α-globin coding sequence. Results obtained in these additional experiments proved the initial observation (Fig. 3C).

Shorter α-Globin Peptides of 75, 65, and 34 Amino Acid Residues Display a Weaker or Nonspecific Cotranslational Heme Binding—As shown previously in in vitro experiments, the proteolytic fragment of the β-globin molecule comprising residues 31–104 is capable of binding the heme group (50). The same phenomenon has been also demonstrated recently for the mini-myoglobin polypeptide fragment (residues 32–139) (51). To determine the length of a globin chain sufficient and necessary for cotranslational heme binding, we translated truncated α-globin mRNAs (Fig. 1) and produced shorter nascent peptides of 75, 65, and 34 amino acid residues. Incorporation of radio-labeled methionine as well as hemin into the nascent globin peptides was controlled after sucrose gradient centrifugation of the wheat germ translation system as described above. In contrast to the experiments with longer polypeptides (Fig. 3, A and B), we found much lower incorporation of [3H]hemin either into the ribosome-bound polypeptides of 34 (not shown), 65, or 75 amino acid residues (Fig. 3, D and E).

Since all polypeptides under investigation have an equal number of methionine residues (at positions 1 and 33), the [3H]hemin/[35S]methionine ratio can be used as a measure of the efficiency of heme binding to the nascent polypeptides of various lengths. Fig. 4 presents the summary of puromycin effects on the release of nascent 35S-labeled methionine polypeptide and [3H]hemin from ribosomes after the translation of full-length and truncated mRNAs. Some amounts of heme found attached to the shorter peptides can probably be attributed to a nonspecific heme adsorption. Alternatively, one can speculate that heme begins to dock to the globin polypeptide chain very early during its synthesis when the first amino acid residues competent for heme binding appear from the peptidyltransferase center, but at these stages the heme binding is not strong enough to form a stable heme-globin complex.

A number of experimental findings suggest cotranslational protein folding (16–28, 32, 52). Thus, the possibility of cotranslational ligand binding cannot be excluded. Studies of biosynthesis of protein D1 of the membrane-bound chloroplast reaction center directly indicated the cotranslational binding of chlorophyll to an incomplete D1 molecule (53, 54). Cotranslational binding was also assumed to take place for the heme group in the case of globins (29, 55). It is well known that the detachment or displacement of heme groups is accompanied by denaturation of hemoglobin, whereas the addition of the heme group to apohemoglobin or apomyoglobin promotes the formation of the native structure of the molecules (30, 56–58). It was shown that mini-apo-β-globin (residues 31–104) or mini-apomyoglobin (residues 32–139) reconstituted with natural heme preserved conformations similar to those in the whole molecules (50, 51). Moreover, it was evident that the heme orientation in the pocket and the coordination state of the ferrous iron in the mini-globins are just the same as in the whole molecules (51). On the grounds of these data we suggest that heme binding to the nascent globin chains can be used as a test of cotranslational folding of globins. The aim of this work is to determine the length of the nascent globin chain on which heme attachment occurs during translation.

We have demonstrated an equally efficient cotranslational incorporation of [3H]hemin into nascent globin chains of 140, 100, and 86 amino acid residues (as well as into the full-length molecule). The fact that puromycin (known to release ribosome-bound peptides) causes the release of both 35S-labeled methionine polypeptide and [3H]hemin from ribosomes (Figs. 2 and 3) indicates that either the nascent peptide of 86 amino acid residues possesses a spatial structure allowing its proper interaction with the heme group or the heme attachment promotes the formation of the proper tertiary structure. Hence, the cotranslational formation of the spatial structure of globin at the early stages of its synthesis is likely. It was recently shown that chemically synthesized peptides with chymotrypsin inhibitor-2 growing from the N terminus acquire the three-dimensional structure in vitro while achieving the length of 62–63 amino acid residues (59). We believe that the same occurs in
the case of nascent α86 (and longer) globin polypeptides growing on the ribosome.

To illustrate our results, we present wire frame models of the well known three-dimensional structures of the human deoxyhemoglobin α-chain (Fig. 5A and Ref. 60) and the incomplete α86-globin chain (Fig. 5B). The α86-globin model was produced from the crystal structure of α-chain by skipping the C-terminal residues. The length of the incomplete α86 molecule in the model is the same as the lengths of nascent peptides in our experiments. There are a number of amino acid residues in the α-globin molecule known to be involved in the formation of contacts with the heme group. Among them are Met-32, Tyr-42, Phe-43, His-45, Phe-46, Lys-61, Val-62, Ala-65, Leu-83, Leu-86, Leu-91, Val-93, Asn-97, Phe-98, Leu-101, Leu-136, and two heme-binding His residues, His-58 and His-87 (60). Our results show that the nascent peptide of 86 amino acid residues lacking the heme-binding histidine residue at position 87 is capable of heme binding. This may indicate that the contacts provided by the remaining residues are sufficient for specific heme binding. Eleven residues involved in heme binding remain in the incomplete polypeptide of 86 amino acid residues (Fig. 5B). Since the incomplete nascent peptide of 75 amino acid residues does not bind the heme group so efficiently (Fig. 3D), it can be speculated that the leucine residues at positions 83 and 86 provide the necessary contacts, thus forming part of the heme pocket and allowing the incomplete nascent chain of 86 amino acid residues to bind the heme group quite effectively.

If this is the case, all the C-terminal sections of the polypeptide must appear from the ribosome and form E and F helices. It presumes that a nascent polypeptide chain can fold immediately at the peptidyltransferase center of the ribosome and no intraribosomal tunnel exists, as was indicated previously (61–63).

The alternative case could be that a ribosomal tunnel or channel hides the C-terminal section of a growing polypeptide (64, 65). Then the nascent ribosome-bound globin peptide of 86 amino acid residues should be able to bind hemin either without F helix, if just 15 amino acid residues are hidden (41, 42), or without both E and F helices, if 30–40 amino acids are accommodated within the ribosome (39, 42, 44). The latter seems unlikely. Rather, the shielding of the C-terminal part of the growing nascent peptide can now be explained by nascent polypeptide-associated complex binding (63, 66), known to protect about 30 C-terminal amino acid residues from the proteolysis. As nascent polypeptide-associated complex cycle of binding and release was proposed (63), it can be speculated that nascent polypeptide-associated complex is released from the nascent peptides when it acquires the three-dimensional structure.
Taking into account all the facts and considerations mentioned above, we argue that the globin polypeptide chain begins to correctly fold with the participation of heme rather early during its elongation on the ribosome.

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