Proteins with expanded polyglutamine domains cause eight inherited neurodegenerative diseases, including Huntington’s, but the molecular mechanism(s) responsible for neuronal degeneration are not yet established. Expanded polyglutamine domain proteins possess properties that distinguish them from the same proteins with shorter glutamine repeats. Unlike proteins with short polyglutamine domains, proteins with expanded polyglutamine domains display unique protein interactions, form intracellular aggregates, and adopt a novel conformation that can be recognized by monoclonal antibodies. Any of these polyglutamine length-dependent properties could be responsible for the pathogenic effects of expanded polyglutamine proteins. To identify peptides that interfere with pathogenic polyglutamine interactions, we screened a combinatorial peptide library expressed on M13 phage pII protein to identify peptides that preferentially bind pathologic-length polyglutamine domains. We identified six tryptophan-rich peptides that preferentially bind pathologic-length polyglutamine domain proteins. Polyglutamine-binding peptide 1 (QBP1) potently inhibits polyglutamine protein aggregation in an in vitro assay, while a scrambled sequence has no effect on aggregation. QBP1 and a tandem repeat of QBP1 also inhibit aggregation of polyglutamine-yellow fluorescent fusion protein in transfected COS-7 cells. Expression of QBP1 potently inhibits polyglutamine-induced cell death. Selective inhibition of pathologic interactions of expanded polyglutamine domains with themselves or other proteins may be a useful strategy for preventing disease onset or for slowing progression of the polyglutamine repeat diseases.

Eight inherited neurodegenerative diseases, including Huntington’s disease, dentatorubral pallidolysian atrophy, spinobulbar muscular atrophy, and spinocerebellar ataxia types 1, 2, 3, 6 and 7, are caused by expanded CAG repeats in the coding region of the disease genes (1–3). The CAG codon is translated into glutamine, and the polyglutamine domain is the only region of homology among the eight disease proteins. The length of the repeat is the critical determinant of age-of-disease onset, with repeat length greater than 40 glutamines producing neurodegeneration in seven of the eight diseases (1–3).

Proteins with pathologic-length polyglutamine domains display novel properties that are not present in these proteins when they contain a shorter polyglutamine domain. Length-dependent polyglutamine-protein interactions are reported for Huntington-associated protein 1, glyceraldehyde-3-phosphate dehydrogenase, leucine-rich acidic nuclear protein, vimentin, neurofilament, apopain, calmodulin, WW domain proteins, and Ras-related nuclear protein ARA24 (4–12). Proteins with expanded polyglutamine domains also aggregate, and aggregation is a pathologic hallmark of the polyglutamine repeat diseases (13, 14). These polyglutamine length-dependent properties may arise from the ability of long polyglutamine domains to adopt unique three-dimensional conformations and serve to confer the disease proteins with a pathologic gain of function (15, 16).

Lansbury proposed that during the initial stages of folding of expanded polyglutamine proteins, misfolded intermediates interact with themselves (homologous interactions) or other proteins (heterologous interactions), leading to critical cell injury (16). Supporting this hypothesis of length-dependent alteration in tertiary structure, Trottier et al. (17) identified a monoclonal antibody (1C2) that preferentially recognizes proteins with long, but not short, polyglutamine domains. Since monoclonal antibody 1C2 recognizes the unique conformation of long polyglutamine domains, we reasoned that peptides with similar polyglutamine-binding properties could be identified by screening peptide libraries. Peptides that selectively bind pathologic-length polyglutamine domains may inhibit interaction with other proteins, thereby slowing, or preventing, disease pathology. In this paper, we identify several polyglutamine-binding peptides and demonstrate the ability of one of these peptides to inhibit polyglutamine aggregation both in a novel in vitro assay and in cultured cells. We further demonstrate that expression of a tandem repeat of a polyglutamine-binding peptide in cell culture inhibits polyglutamine-induced cell death.

MATERIALS AND METHODS

Phage Display Screening—Phage display library construction and screening were performed as described (18, 19). Brieﬂy, 53-mer nucleotides were ligated to the S′ terminus of the pII gene of phage M13 to generate a peptide library with 11 amino acids added to the amino terminus of the pIII protein. Individual phage libraries were screened for binding to a polyglutamine-glutathione S-transferase fusion protein with 62 glutamines (Q62-GST). Construction of the polyglutamine-GST vectors was described previously (20). Q62-GST was immobilized on...
Identification of Peptides That Preferentially Bind Protein with a Pathologic-Length Polyglutamine Domain—We screened a peptide phage display library to identify peptides that interact with proteins containing a pathologic-length polyglutamine domain. The M13 phage display library was constructed to contain a random 11-amino acid peptide inserted at the amino terminus of the pIII capsid protein (18). The 11-mer peptide was not completely random, since a fixed amino acid was inserted in the sixth position of the peptide (X₆-fixed-X₆) to decrease the vast number of possible peptides (20₁¹) and permit more thorough sampling. 2.5 × 10₁¹ phage from each of the following fixed amino acid libraries were screened for binding to a polyglutamine-glutathione S-transferase fusion protein with 62 glutamines (Q₆₂-GST); aspartate, phenylalanine, histidine, lysine, leucine, proline, and tryptophan (19, 21). After four rounds of successive screening, 350 polyglutamine-binding phage clones were isolated. The selected peptide was then assayed by enzyme-linked immunosorbent assay for binding to normal length (Q₁₉) or pathologic-length (Q₆₂) polyglutamine-GST. Six phage clones bound Q₆₂-GST greater than Q₁₉-GST (binding ratios of Q₆₂-GST to Q₁₉-GST: 1.23–1.66) and had their DNA sequenced to elucidate peptide sequence (Table I; QBP1–6).

| Sequence (X₆-fixed-X₆) | Q₆₂/Q₁₉ binding ratio | Name |
|------------------------|-----------------------|------|
| SNNKKWPGIFD            | 1.66                  | QB1  |
| HWMRSHSDESY            | 1.31                  | QB2  |
| HENHWHQGEAA            | 1.30                  | QB3  |
| WGLHEHAGKNR            | 1.27                  | QB4  |
| WRWNGATFVD             | 1.25                  | QB5  |
| WHNFYWQRQDT            | 1.23                  | QB6  |
| WPINSKGDFWF            |                       | SCR  |
| LSLSMEPCCGGA           |                       | RAN  |
| SNNKKWPGIFDWNNKWKPGIFD |                       | QBP1₂|

In Vitro Aggregation of Thioredoxin-Polyglutamine—We then developed an in vitro aggregation assay to examine whether these polyglutamine-binding peptides inhibit polyglutamine aggregation. Polyglutamine-GST proteins are not ideal for studying polyglutamine aggregation, since the polyglutamine domain does not aggregate unless it is cleaved from the GST moiety (22, 23). To circumvent this limitation, we produced thioredoxin-polyglutamine fusion proteins (thio-Qₙ; where n = the number of consecutive glutamine residues). Thioredoxin is highly soluble, can be expressed at high concentrations in E. coli, and is easily purified (24). The length of the expressed glutamine domains was chosen to survey a range of normal and pathologic peptide repeat lengths (normal: 19 and 35 glutamines; pathologic: 62 and 81 glutamines) (Fig. 1A).

To monitor thioredoxin-polyglutamine protein aggregation, we developed a turbidometric assay, similar to the assays commonly used to study microtubule assembly and β-amyloid aggregation (25, 26). Solutions of thio-Q₆₂ and thio-Q₈₁ protein increased turbidity in a polyglutamine length-, time-, and concentration-dependent manner (Fig. 1B and C; time dependence of aggregation of thioredoxin-polyglutamine with 81 glutamines is not shown). To demonstrate that turbidity was produced by aggregation of thioredoxin-polyglutamine protein containing 62 or 81 glutamines (thio-Q₆₂ or thio-Q₈₁), we pelleted the insoluble material by centrifugation or captured it on a 0.22-μm filter. The pelleted and retained material was confirmed as thioredoxin-polyglutamine fusion protein containing 62 or 81 glutamines on Western blots probed with anti-thioredoxin or anti-polyglutamine antibody (not shown). In contrast, thioredoxin-polyglutamine protein containing 19 or 35 glutamines was not completely random, since a fixed amino acid was inserted in the sixth position of the peptide (X₆-fixed-X₆) to decrease the vast number of possible peptides (20₁¹) and permit more thorough sampling. 2.5 × 10₁¹ phage from each of the following fixed amino acid libraries were screened for binding to a polyglutamine-glutathione S-transferase fusion protein with 62 glutamines (Q₆₂-GST); aspartate, phenylalanine, histidine, lysine, leucine, proline, and tryptophan (19, 21). After four rounds of successive screening, 350 polyglutamine-binding phage clones were isolated. The selected peptide was then assayed by enzyme-linked immunosorbent assay for binding to normal length (Q₁₉) or pathologic-length (Q₆₂) polyglutamine-GST. Six phage clones bound Q₆₂-GST greater than Q₁₉-GST (binding ratios of Q₆₂-GST to Q₁₉-GST: 1.23–1.66) and had their DNA sequenced to elucidate peptide sequence (Table I; QBP1–6).
Inhibition Polyglutamine Protein Aggregation and Cell Death

In vitro. We synthesized the 11-mer peptide with the greatest polyglutamine binding peptides on polyglutamine aggregation next examined the effect of these combinatorially generated peptides had no effect on the turbidity of the nonpathologic thioredoxin-polyglutamine proteins with 19 or 35 glutamines (thio-Q19, thio-Q35 not shown).

QB1 Co-localizes with Polyglutamine Aggregate in Cells—We next determined whether QB1 also inhibits polyglutamine aggregation in transfected COS-7 cells. As we previously demonstrated, COS-7 cells expressing polyglutamine domain fusion proteins are a good cellular model of the polyglutamine repeat diseases because the polyglutamine-fusion proteins mimic the native disease proteins by forming aggregates and by killing cells in a polyglutamine length-dependent pattern (7).

To determine the intracellular distribution of both polyglutamine and QB1, we designed fusion proteins of polyglutamine with yellow fluorescent protein (Qn-YFP, where n = 19, 45, 57, or 81 glutamines) and fused QB1 with cyan fluorescent protein (QB1-CFP) (Fig. 3A). YFP and CFP are variants of green fluorescent protein with distinct emission spectra, which enable separate detection of each fluorescent protein in double labeled cells (27).

QB1 fused to cyan fluorescent protein (QB1-CFP) expressed in COS-7 cells remained diffusely distributed (not shown). A polyglutamine-yellow fluorescent protein fusion protein with 19 glutamines (Q19-YFP) was also diffusely distributed, and its distribution was unaffected by co-expression with QB1-CFP (Fig. 3B, a and b). Expression of a pathologic-length polyglutamine-YFP fusion protein with 81 glutamines (Q81-YFP) in transfected cells formed aggregate. Co-expression of Q81-YFP and QB1-CFP produced co-localization of these two fluorescent proteins in the protein aggregates (Fig. 3B, c and d). In contrast, random peptide or scrambled peptide fused to CFP (RAN-CFP and SCR-CFP) did not co-localize with the aggregate formed by Q81-YFP (Fig. 3B, e–h).

QB1 Inhibits Polyglutamine Aggregate Formation in Cells—We next examined the effect of QB1-CFP expression on Qn-YFP aggregate formation in co-transfected COS-7 cells. Diffuse fluorescence was easily distinguishable from aggregate using the fluorescence microscope (compare diffuse fluorescence of polyglutamine in Fig. 3B, a, with punctate fluorescence of aggregated protein in Fig. 3B, c, e, and g). Co-expression of QB1-CFP reduced the percentage of cells with polyglutamine aggregates (Fig. 4). Inhibition of polyglutamine aggregation by QB1-CFP was most pronounced with shorter pathologic-length glutamine fusion proteins (45 glutamines (Q45) > 57 glutamines (Q57) > 81 glutamines (Q81)). Compared with cells co-expressing RAN-CFP, QB1-CFP reduced aggregation of Q45-YFP by 39% (Fig. 4; p < 0.01). QB1 also reduced aggregation of Q57-YFP by 26% (p < 0.01). A trend toward decreasing aggregation was seen in cells transfected with QB1 and Q57-YFP, but the difference did not reach statistical significance (p = 0.073). The decline in QB1-CFP’s ability to inhibit ag-
aggregation of proteins with increasingly long polyglutamine domains in cells is consistent with our in vitro data showing that QBP1 is less effective at inhibiting aggregation of thio-Q62 compared with thio-Q57. To determine if duplication of the sequence of QBP1 would affect its ability to inhibit polyglutamine aggregation, we prepared a tandem repeat of QBP1 fused to CFP. (QBP1)_2-CFP is more effective at inhibiting all lengths of polyglutamine-YFP aggregation than monomer QBP1-CFP (Fig. 4, dotted bars). SCR-CFP did not alter aggregation of cells expressing polyglutamine-CFP with 45, 57, or 81 glutamines (Q45-, Q57-, or Q81-YFP) (Fig. 4, hatched bars).

Polyglutamine Binding Peptide Inhibits Cell Death—The relationship between polyglutamine protein aggregation and cell death is controversial. To determine whether QBP1 or tandem-QBP1 inhibit polyglutamine-induced cell death, we assayed cell membrane permeability to ethidium homodimer. The mem-

Fig. 2. Polyglutamine binding peptide inhibition of thioredoxin-Q62 aggregation. QBP1 inhibits thio-Q62 aggregation in a concentration-dependent pattern (filled bars). RAN (open bar) and SCR (hatched bar), at 25 μM, inhibited thio-Q62 aggregation less than 10%. Aggregation was assayed by turbidity at 405 nm (13). Results shown are from representative experiments (n = 4). Variation between duplicate wells was less than 10%.

Fig. 3. Intracellular distribution of Qn-YFP and QBP1-CFP in COS 7 cells. A, schematic representations of Qn-YFP (upper) and QBP1-, RAN-, or SCR-CFP fusion proteins (lower). B, fluorescent micrographs demonstrating co-localization of QBP1-CFP with Q62-YFP aggregates in COS 7 cells 48 h after transfection. a and b, co-expression of Q19-YFP and QBP1-CFP; c and d, Q31-YFP and QBP1-CFP; e and f, Q45-YFP and RAN-CFP; g and h, Q62-YFP and SCR-CFP. a, c, e, and g, images obtained by YFP filter set (Omega Optical). b, d, f, and h, images obtained by CFP filter set (Omega Optical). No YFP signal could be seen using the CFP filter, and no CFP fluorescence was detected using the YFP filter. Magnification was ×320.

Fig. 4. QBP1 expression decreases the number of cells containing polyglutamine aggregates. Open bar, cells co-transfected with Qn-YFP and RAN-CFP. Hatched bar, cells co-transfected with Qn-YFP and SCR-CFP. Filled bar, cells co-transfected with Qn-YFP and QBP1-CFP. Dotted bar, cells co-transfected with Qn-YFP and (QBP1)_2-CFP. COS-7 cells were examined 48 h after transfection using a Zeiss fluorescence microscope with the CFP/YFP filter set from Omega Optical. The percentage of cells with aggregates was calculated by counting the number of transfected cells containing aggregate and dividing by the total number of transfected cells multiplied times 100. In each experiment, at least 200 transfected cells were counted. Experiments were repeated at least four times. Error bars represent S.E. *, p < 0.05; **, p < 0.01 (Student’s t test).
branes of living cells are impermeable to ethidium homodimer, and permeability to ethidium homodimer is a well established measure of cell death (28, 29). Ethidium homodimer undergoes a 30-fold increase in fluorescence upon binding to nucleic acid, allowing easy detection with a fluorescence microscope using a rhodamine filter. QBP1 and (QBP1)_2 fused to CFP inhibit Q57-YFP-induced cell death (Fig. 5). As with inhibition of aggregation, (QBP1)_2 is more effective at inhibiting cell death than monomer QBP1. Similar results have also been observed with Q45- and Q81-YFP (not shown). Scrambled QBP1 fused to CFP (SCR) does not inhibit cell death (Fig. 5).

**DISCUSSION**

No therapies modify the age-of-onset of symptoms or pathologic progression of the polyglutamine repeat diseases. In this paper, we identified a novel peptide that is a therapeutic prototype because it preferentially binds pathologic-length polyglutamine domains, inhibits polyglutamine aggregation both in vitro and in cultured cells, and reduces cell death. In addition, we described an in vitro, high throughput, polyglutamine aggregation assay that can be used to identify small molecules that inhibit aggregation.

The combinatorially generated peptides identified by phage display screening that preferentially bind pathologic-length polyglutamine domains (QBP1–6) have a conserved motif; the peptides are tryptophan-rich (5 of 6) and most include a cluster of 3 tryptophans, including a pair of adjacent tryptophans. Peptides containing tandem tryptophans also contain an adjacent basic (positively charged) amino acid. QBP1 has no homology with other proteins that bind polyglutamine domain proteins, including glyceraldehyde-3-phosphate dehydrogenase, neurofilament, vimentin, Huntington-associated protein 1, SH3-GL3, or WW domain proteins (4, 5, 7, 8, 11, 30, 31).

Inhibition of in vitro and intracellular polyglutamine protein aggregation by QBP1 is sequence-specific, since a scrambled version of the QBP1 peptide had no effect on aggregation. Binding to proteins with expanded-length polyglutamine domains or inhibition of polyglutamine aggregation by QBP1 is robust and is observed whether the peptide is free or fused to the M13 phage protein or to CFP. QBP1 binds to polyglutamine whether the polyglutamine domain is fused to GST, thioredoxin, or YFP, suggesting that polyglutamine-binding peptides would interact with the expanded polyglutamine domain in disease proteins, such as huntingtin.

Our data further demonstrate that QBP1 inhibits polyglutamine-induced cell death. QBP1-CFP expression inhibited Q57-YFP-induced cell death by 19%, and tandem QBP1 inhibited cell death by 50%.

Despite the almost universal presence of polyglutamine aggregates in the polyglutamine repeat diseases, the role of aggregation itself in pathogenesis is controversial. Polyglutamine protein aggregates may cause neurodegeneration or form as a response to cell injury. Igarashi et al. (32) demonstrated that inhibition of aggregation by transglutaminase inhibitors partially blocked apoptotic cell death. Similarly, Chai et al. (33) found that overexpression of chaperone protein HDJ-1 in PC12 cells inhibited polyglutamine protein aggregation and toxicity. In contrast, others have found that aggregation and cell death are separate phenomena (34). Klement et al. (35) found that deletion of the self-association of ataxin 1 blocked aggregation but not cell death. Similarly, Saudou et al. showed that cell death induced by mutant huntingtin was not directly correlated with intranuclear aggregate formation (36). Whatever the function of aggregates, interaction of pathologic-length polyglutamine proteins with themselves or other proteins may disrupt critical cellular processes and destroy homeostasis. In our experiments, decreased aggregation parallels the decline in toxicity, but this does not prove that decreased toxicity is mediated by decreased aggregation. QBP1 may be exerting its effect by inhibiting interactions of polyglutamine proteins with other molecules, and the decrease in aggregation may be an epiphenomenon.

A limiting factor to identifying new therapeutic agents for these diseases is the lack of a high throughput screening assay. Aggregation of polyglutamine proteins in vitro has been previously described, but these assays either require proteolytic cleavage of polyglutamine fusion proteins or employ detection systems (such as dynamic light scattering) not readily adaptable for rapid screening (23, 37). In this paper, we describe a new, simple, in vitro assay of polyglutamine aggregation that facilitates the identification of compounds that inhibit aggregation. Aggregation of thi-Q45 protein in vitro faithfully recapitulates the behavior of polyglutamine proteins in human disease. As shown here, thi-Q45 aggregation occurs in vitro only with repeats longer than 35; in Huntington’s disease, the most common polyglutamine repeat disease, individuals develop disease only if they express a huntingtin protein with more than 36 sequential glutamines (38). In vitro, thi-Q45 protein with longer pathologic-length polyglutamine domains aggregates more rapidly and at lower concentration than with shorter pathologic-length glutamine domains; similarly, in Hunting-
ton’s disease, polyglutamine domain length directly correlates with earlier age of onset, severity of clinical phenotype, and aggregate formation (39). The ability to identify compounds that selectively alter intracellular interactions and metabolism of pathologic-length polyglutamine domain proteins may be an effective therapeutic strategy in these diseases.

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Inhibition Polyglutamine Protein Aggregation and Cell Death
Inhibition of Polyglutamine Protein Aggregation and Cell Death by Novel Peptides Identified by Phage Display Screening
Yoshitaka Nagai, Timothy Tucker, Hongzu Ren, Daniel J. Kenan, Barry S. Henderson, Jack D. Keene, Warren J. Strittmatter and James R. Burke

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