Unfolded Protein Binding

Annotation Review

Reclassifying GO:0051082 & GO:0031249

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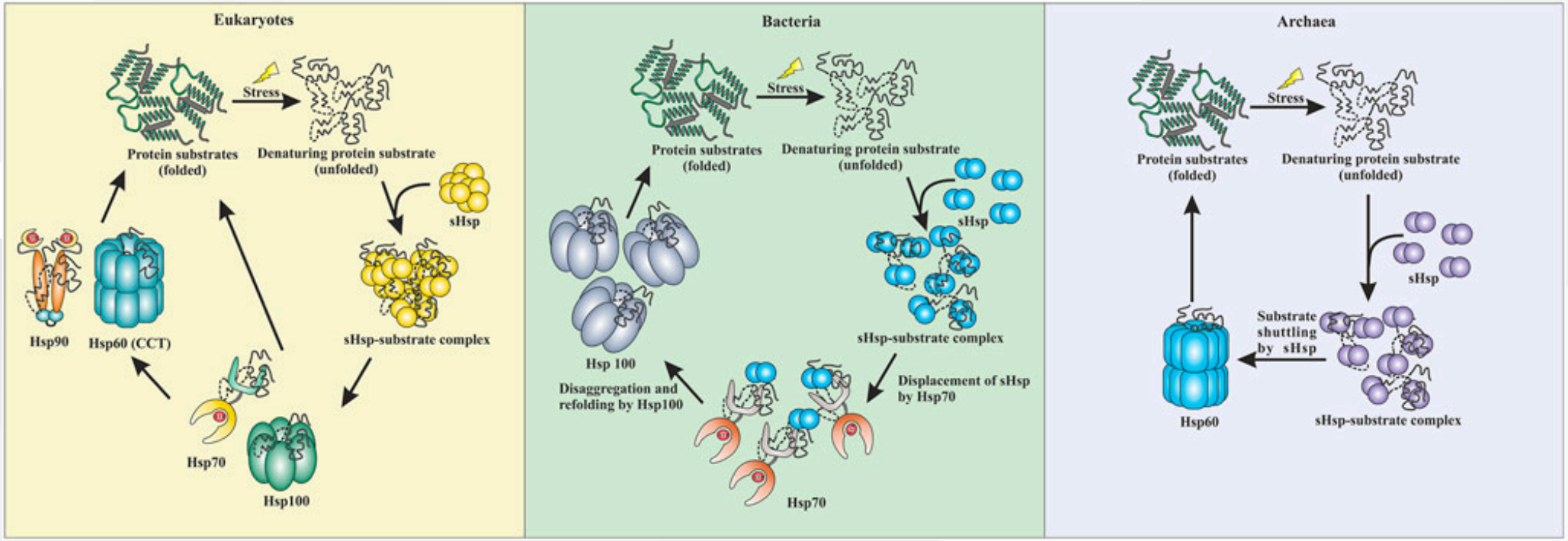
The Problem

GO:0051082 "unfolded protein binding" and **GO:0031249** "denatured protein binding" proposed for obsoletion (go-ontology#30962)

These terms conflate mechanistically distinct activities under a single "binding" label:

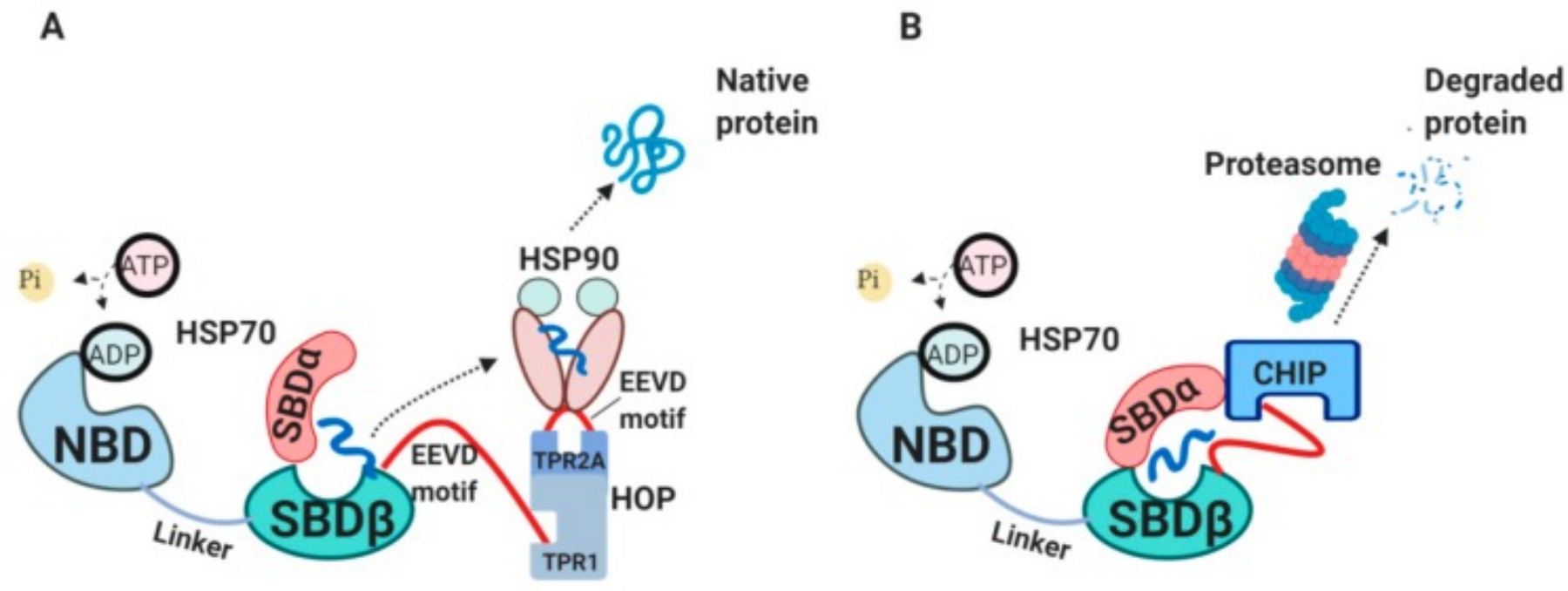
- ATP-dependent **foldases** that actively refold clients
- ATP-independent **holdases** that prevent aggregation in situ
- **Disaggregases** that solubilize existing aggregates
- **Sensors** that recognize misfolded proteins for degradation
- **Co-chaperones** that modulate chaperone ATPase cycles

The Holdase-Foldase Network



Conserved across all domains of life: stress unfolds proteins; **sHSPs (holdases)** capture them to prevent aggregation; clients are handed off to **Hsp70 (foldase)** for ATP-dependent refolding, or to **Hsp100 (disaggregase)**. Eukaryotes also use Hsp90 and Hsp60/CCT.

The Proteostasis Triage Decision



(A) HSP70-HOP-HSP90 axis: fold-forward pathway to native protein.

(B) HSP70-CHIP axis: ubiquitination and proteasomal degradation.

Co-chaperones (DNAJ, NEFs, BAG1/3) tune the **fold vs degrade** decision.

Figure 2 from Radons (2020) *Cells* 9:587, CC-BY 4.0

Recent Literature Context

Key reviews informing this reclassification:

- Mitra et al. (2022) *Annu Rev Biophys* 51:409 — ATP-independent chaperones; force-clamp experiments show context-dependent holdase/foldase switching
- Bhattacharjee et al. (2025) *J Biosci* — Co-chaperones fine-tune HSP70: fold, hold, or degrade; O-GlcNAc modification of HSP27 promotes BAG3-mediated refolding
- Boopathy (2024) — HUWE1 + HSP70 cooperate to clear nuclear inclusions, linking holdase activity to E3-mediated clearance
- Le et al. (2024) *Mol Cells* — UBR1/UBR2 as ER-stress sensors: substrate load stabilizes these E3s to enhance PQC

Scope of This Review

Metric	Count
Unique genes reviewed	**148**
Human genes (primary)	33
Non-human genes	115
Species covered	17
Total annotations reviewed	**5,529**
Remaining PENDING	**0**

All experimental annotations to GO:0051082/GO:0031249 across all species.

Mechanism Classes

Class	GO term	ATP?	Example
Foldase	GO:0044183	Yes	GroEL/ES, TRiC/CCT
Holdase	*NTR needed*	No	CRYAB, CLU
Carrier-holdase	GO:0140309	No	Tim9-Tim10
Foldase/holdase	GO:0044183 + holdase NTR	Yes	HSPA1A (HSP70)
Co-chaperone	*(see gap)*	N/A	DNAJB1, AHSA1
Disaggregase	GO:0140545	Yes	HSP104, HSPA1A
Sensor	*NTR proposed*	N/A	SYVN1, UGGT1

Decision Rules

Mechanism	Action	Replacement
Foldase (GroEL, TRiC)	MODIFY	GO:0044183
Foldase/holdase (HSP70)	MODIFY	GO:0044183 *(holdase NTR pending)*
Co-chaperone, J-domain	MODIFY	GO:0044183 *(interim)*
Holdase (sHSP, crystallin)	MODIFY	holdase NTR *(retain GO:0051082)*
Disaggregase	MODIFY	GO:0140545
ER/QC sensor	REMOVE	*(not chaperones)*
HSP90 co-chaperone	OVER_ANNOTATED	*(not direct UPB)*

Impact: Human Genes (n=33)

Primary action	Count	Notes
MODIFY to GO:0044183 (foldase)	16	HSP70 (6), J-domain interim (4), prefoldin (6)
MODIFY to holdase NTR	7	sHSPs, CLU, SCG5, DNAJB6, DNAJB8
MODIFY to other specific MF	2	NPM1, AIP
MARK_AS_OVER_ANNOTATED	5	Sensor/co-chaperone cases
REMOVE	3	SYVN1, ERLEC1, GRPEL1

Plus 3 co-annotations to GO:0140545 (disaggregase): HSPA1A, HSPA1B, HSPA8

Before/After Examples

Gene	Before	After	Why
HSPA1A	GO:0051082	GO:0044183 + GO:0140545	ATP-dependent foldase + disaggregase
CRYAB	GO:0051082	holdase NTR	sHSP holdase; prevents aggregation in situ
DNAJB1	GO:0051082	GO:0044183 *(interim)*	J-domain co-chaperone, not independent foldase
SYVN1	GO:0051082	REMOVE	E3 ligase; recognizes misfolded substrates
NPM1	GO:0051082	GO:0140713	Histone chaperone; UPB was secondary

Critical Finding: The Holdase Gap

GO:0140309 "unfolded protein carrier activity" does **not** fit most holdases.

- Created Nov 2025 for TIM carrier-holdases (Tim9-Tim10) in go-ontology#30552
- Definition requires escort "between two different cellular components"
- "holdase" is a **BROAD** synonym (not exact) on GO:0140309
- Val acknowledged a general holdase term was needed but deferred it

7 human genes + HSPH1 are in-situ holdases that prevent aggregation without inter-compartment escort. They cannot use GO:0140309.

Proposed: "Holdase Chaperone Activity"

Definition: Binding to an unfolded or misfolded protein to prevent its aggregation without actively catalyzing refolding. The holdase maintains the client protein in a soluble, folding-competent state.

Parentage: Direct child of GO:0003674 (molecular_function).
GO:0140309 (carrier-holdase) becomes a child of this new term.

Affected genes: CRYAA, CRYAB, HSPB6, CLU, SCG5, DNAJB6, DNAJB8, HSPH1

GO:0051082 **obsoletion must be blocked until this NTR exists.**

Other Ontology Gaps

Misfolded protein sensor activity

- Recognition of misfolded conformation for QC degradation
- CHIP/STUB1 ubiquitinates chaperone-bound clients; UBR1/UBR2 recognize N-degrons (Le et al. 2024)
- Affects: SYVN1, SAN1 (yeast), Fbxo2 (mouse)

Co-chaperone MF representation

- GO:0003767 "co-chaperone activity" deliberately obsoleted
- No MF term for J-domain co-chaperone function (ATPase activation + substrate delivery)
- GO:0044183 used as pragmatic interim
- Affects all J-domain proteins across species

Cross-Species Validation

The same mechanism classes apply universally across 17 species.

Species	Genes	Highlights
S. cerevisiae	67	All 14 mechanism classes represented
E. coli	13	Periplasmic holdases (SurA, Skp, Spy, HdeA/B)
D. melanogaster	7	sHSPs Hsp22-27
M. musculus	6	Hspa8 largest review (240 annotations)
R. norvegicus	4	Hspa5/BiP (101 annotations)
Other (12 spp.)	18	Zebrafish crystallins, CnoX redox holdase

Notable Cross-Species Findings

- **SlrP** (*S. typhimurium*): **misannotation removed** — T3SS effector E3 ligase, not a chaperone
- **CnoX** (*E. coli*): redox-activated holdase — becomes active under oxidative stress when Cys residues are oxidized
- **Peroxiredoxins** (TSA1, pmp20, tpx1): dual-function — peroxidase at low stress, holdase at high stress (overoxidation switch)
- **Assembly factors** (ATP10, PET100, COX20): single-client chaperones, not general UPB — all OVER_ANNOTATED
- **IRE1** (yeast + *T. reesei*): UPR sensor, not chaperone — cross-kingdom confirmation

What We Need from GO Editors

1. **Holdase NTR (BLOCKING)**: Create "holdase chaperone activity" for in-situ holdases
2. **Block** GO:0051082 **obsoletion** until holdase NTR exists (7 genes have no replacement)
3. **Preferred labels**: "foldase" exact synonym on GO:0044183; "holdase" exact on new term
4. **Co-chaperone MF gap**: How should J-domain function be annotated?
5. **HSP70 dual annotation**: Confirm foldase + holdase per experimental context
6. **Misfolded protein sensor**: New term for SYVN1, SAN1, Fbxo2?

Summary

148 genes across **17 species**, **5,529 annotations** reviewed

The key bottleneck is the **holdase NTR** — without it, 7+ genes cannot be reannotated and GO:0051082 obsoletion is blocked.

All gene review YAMLs: `genes/<SPECIES>/<GENE>/`
Validate: `just validate-all`