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The Elimination of Mutations by the Cell's Elaborate Protein Quality Control Factory: A Major Problem for Neo-Darwinism

Jerry Bergman*

Abstract

Proper protein folding requires specific "chaperones" and other molecular machinery called "folding factors." Both the genomic code and the folding machinery are required in order to produce a functional protein. The cell also has an elaborate quality control system to ensure that the cellular parts are manufactured to the required specifications. Recent research has added new levels of complexity to our current level of understanding of cell biology quality control. One important role of this newly discovered system is the removal and recycling of improperly folded proteins caused by any number of factors including mutations. Mutations are assumed by neo-Darwinists to be the ultimate source of all new genetic information. In order to produce a new protein by mutations, however, both appropriate folding and quality control systems also must adapt. Without them, a mutant is useless, even if it produces a selective advantage. Quality control results in many, if not most, mutated proteins being repaired or cut up and recycled, even if they are beneficial to the organism. This detail manifests irreducible complexity that favors intelligent design.

Introduction

Natural selection cannot produce new genetic information, but can only select from what already exists in the genome. Mutation now is believed to be the only significant mechanism capable of producing new genetic information. For this reason, mutations are believed to be the ultimate source of all genetic variety (Mayr, 1967, 2001). According to neo-Darwinism this genetic variety enabled natural selection to evolve all life over vast time periods. But many changes in the DNA base sequence never result in amino acid changes within the protein because several different DNA codons translate the same amino acid. This built-in stability factor has been discussed by Colin Brown (1999, 2000) under the designation of "symmetric variation." Assuming that mutation and natural selection could produce new proteins, a method must evolve simultaneously to process the new proteins properly.

Protein processing is a complex procedure that is just now beginning to be understood (Lee and Yu, 2005; Houry, et al., 1999). It involves folding a newly synthesized amino acid polymer chain into its proper physical shape, called its "conformation." It also requires a complex cellular quality control system present in the cell. The existing system

* Jerry Bergman, Ph.D., Biology Department Northwest State College, Archbold, OH 43502, jbergman@northweststate.edu

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would eliminate many, if not most, new proteins, even if they were beneficial in the organism and even if they conferred a selective advantage. The system exists because many aberrant proteins are extremely harmful to cells and, for this reason, are cut up and recycled (Lee and Yu, 2005; Sitia and Braakman, 2003). Potentially beneficial proteins caused by mutations are also cut up and recycled by the ubiquitin-proteasome degradation system designed to ensure a high fidelity of protein expression (Lee and Yu, 2005). The process of "cutting up" proteins involves enzymes that break the peptide bonds between the amino acids that make up the protein chain. The result is "amino-acid monomers" that are then reused to make other proteins.

Many mutational changes in proteins that might be beneficial are not seen in living organisms because they do not make it through the cell's quality control system, part of which is described below. Many mutations that could be beneficial to an adult block an embryo from progressing past the first cell divisions because the mutant interferes with normal cellular function (Lee and Tsai, 2005). If they pass this hurdle, the systems described below are activated.

Proper Processing Required

Proper protein production required for cell survival and growth requires an elaborate quality control system (Collet and Bardwell, 2002). This system entails the involvement of a host of regulators that function as monitors, ushers, transporters, inspectors, security guards, and "emergency technicians" (Xu, et al., 1997). It is described as "wonderfully complex and highly dynamic ... the details of which are only beginning to emerge" (Lorimer, 1997, p. 720). Research in the decade since Lorimer made this observation has confirmed his prediction. For example, "the number of proteins that can be classified as molecular chaperones" has steadily increased (Lee and Tsai, 2005, p. 259).

Promoting protein assembly requires constantly controlling the flurry of cellular activity necessary to maintain the cellular state of dynamic equilibrium called *homeostasis* (Ellis, 1996; Morimoto, 1996). This control system, together with the cell's elaborate repair system, blocks the expression of nearly all mutations that produced significant conformational changes (Lee and Yu, 2005). This process works against evolution by mutations. A family of illnesses, called conformation diseases, results when certain misfolded proteins escape the degradation process (Lee and Yu, 2005). Examples include amyloidosis, Creutzfeldt-Jakob's disease, scurvy, cystic fibrosis, sickle-cell anemia, Alzheimer's syndrome, and certain other degenerative diseases (Selkoe, 2003).

The Folding Requirement

In the words of Pennisi (1996), a cell is like a "crowded marketplace, with proteins hustling from one job to the next, jostling and potentially interfering with one another along the way" (p. 1613). Proteins consist of hundreds of amino acids that first are sequentially assembled by ribosomes according to a sequence based on the mRNA code template. The long amino acid chains are then folded into specific, intricate, three-dimensional shapes that contain all the twists, turns, folds, pockets, and loops essential for performing the numerous functions required by the cell.

Each protein can fold myriads of different ways, and for this reason require guidance to fold correctly. This guidance is often provided by large complex machine-like molecules called *chaperones*. The chaperones are equipped to properly fold specific proteins or specific types of proteins (Lee and Tsai, 2005; Ellis, et al., 2000). The chaperones are themselves produced by ribosomes according to a code sequence contained in the genes. Other structures also may aid in folding so that there is a whole protein folding system ensuring that newly sequenced proteins are folded into their correct shapes. This is critical because, as noted above, improper folding of a particular protein can produce death or disease.

Johnson (1994) asserted that this entire complex folding system is required because the supposed "age of the Universe is short compared with the time it would take even a small protein to sample the many billion possible folds en route to the right one" (p. 29). As the unfolded protein chain of amino acid residues move toward its final folded form, numerous factors could render it useless because

> amino acids attract all manner of other molecules intent on illicit chemical liaisons. Anyone who has had to deal with unfolded proteins in a test tube knows the hazards only too well: rather than ending up with fully functioning protein molecules, you are more likely to get a glutinous tangled mess, the chemical equivalent of a plateful of overcooked spaghetti. But in cells, proteins do fold correctly, or we wouldn't be here to wonder about them (Johnson, 1994, p. 29).

The folding is double-checked several times by numerous other quality control systems, many of which involve enzymes produced by ribosomes, requiring the proper gene sequence. Mutational changes sufficient to produce a new protein would also likely require a new set of custom chaperones and enzymes to fold the new protein properly. Many mutations may be expected to interfere with this process of quality control and would produce a non-functional protein until the quality control system also evolved to fold and process the new protein properly. In the meantime, the misfolded protein would be recycled or could potentially cause disease or even death.

Some proteins in mammalian cells begin folding with the assistance of specialized chaperones while still being translated, a condition called co-translational folding. This folding occurs in networked tunnels in the endoplasmic reticulum (ER) found throughout the cell near the nucleus. Sequential interactions with a set of specific chaperones often are required for each folding step. Folding is then completed after the protein is produced (called post-translational folding), and individual protein subunits are usually folded before the assembly of multiple different chains, a process known as oligomerization (Sitia and Braakman, 2003).

Final folding is completed inside the ER next to where the protein assembly ribosomes are located. The finished protein is then transported elsewhere by special membrane-bound containers for further processing. The finished protein may perform its role in the body either in the cell or outside, as is the case with secreted proteins. A multitude of other processes involving both software-like and hardware-like systems must all work together to ensure successful protein manufacture. This system would need to be adjusted and/or greatly modified to properly process a new protein produced by mutations (Ibba and Söll, 1999). Some of the sequential interactions and the specifically designed chaperones required for each one of these steps will now be discussed.

Recognition of Correct Folding

Although a strand of amino acid residues can fold in a large number of ways, the chaperones are able to distinguish the one correct way, called the "native folding arrangement" from the many incorrect patterns (Sitia and Braakman, 2003). Chaperones are especially critical in discriminating between native and nonnative protein foldings. Multimolecular complexes, called *folding factors*, provide matrices that couple retention in the ER to proper folding and assembly.

A mechanism exists to help ensure that proteins are not ejected from the ER before they are completely folded. Both when folding occurs, and during assembly, special chemical compounds expose the amino acid's hydrophobic surfaces, unpaired cysteines, or immature glycans, allowing ER-resident chaperones or oxidoreductases to interact with them to help ensure proper folding. As a consequence of this interaction, altered or damaged proteins are retained in the ER or are retrieved from an organelle called the Golgi complex and chauffeured back to the ER to be repaired. The Golgi complex is part of the protein processing and modification system. Incompletely folded proteins can also form aggregates that prevent them from entering the vesicles used to transport properly processed proteins away from the ER. This system works against neo-Darwinian evolution by mutations because "mutations or even unbalanced subunit synthesis make folding or assembly—and hence exit from the ER—impossible" (Sitia and Braakman, 2003, p. 892).

Workforce Regulation

The cell keeps track of how many of *each specific kind* of chaperone is available for use. It uses this information to regulate the number of each chaperone type by sending signals to the nucleus to increase, or decrease, the number of specific chaperones to be produced. To maintain the effectiveness of its quality-control mechanisms in a variety of physiological environments, cells have "regulatory circuits that monitor the levels of available chaperones" in both the cytosol (the cell part that lacks membranes or particulate sub cellular components) and the ER (Sitia and Braakman, 2003, p. 893). Optimal levels of the desired folding factors are also regulated in each area of the cell.

Feedback Regulation

Part of the ER quality control involves sending messages back to the nucleus to help regulate the level of chaperone production. This is a basic, but very important, feedback mechanism.

MicroRNA Regulation Control

MicroRNAs (miRNAs) are small, short strings of RNA existing in large numbers in every cell type. They bind to mRNA molecules in order to regulate their function, either by inhibiting them from making proteins, or by targeting them for destruction (Enright, et al., 2003). Many fundamental development processes are microRNA regulated. For a new protein to exist, it must evolve a compatible microRNA regulation system, or it must be properly regulated by an existing system. Without this system, too much or too little protein will result, causing injury or death to cell or organism.

Location Specificity

Although most folding factors are "ubiquitously expressed throughout the body, some are tissue-type specific or cell-type specific, and probably fulfill a particular synthetic task" (Sitia and Braakman, 2003, p. 891). Collagen is a fibrous protein used for a glue function in connective tissue, bone, skin and cartilage. Efficient collagen production requires the expression of a chaperone called heat shock protein 47 (hsp47). On a wider level, "a tissue-specific protein-disulphide-isomerase-like protein, PDIp, is produced in the pancreas and probably permits the massive secretion of digestive enzymes" (Sitia and Braakman, 2003, p. 891). Heat shock proteins (hsp) are a superfamily of proteins that help to refold proteins in specific locations where heat, acid-base imbalances, or other factors cause distortions (called *denaturations*) of the protein's conformation.

Fail-safe Inspection

After folding, a protein must then successfully pass through multiple layers of monitoring before it can be sent to the location in the cell, or the body as a whole, where it is to be used. Sitia and

Braakman (2003) call this a "fail-safe" inspection system.

Time Limits

The cell is able to determine when a protein has had enough time to fold properly. It must then discriminate between those that have the needed time from those that have not yet folded properly but will do so with more time.

Bridge Builders

Disulfide bridges are one of the four types of chemical bonds used to produce the final stable protein structure. Sulfur bonds are commonly used to stabilize protein folds and must be maintained by a host of oxidoreductase enzymes. The large number of oxidoreductases in the ER indicates that regulation of disulfide-bond formation is critical for proper folding. A disulfide bond is a weak bond, only slightly stronger than that of a single hydrogen bond, yet these bonds are crucial to produce native conformations for many proteins because the disulfide bond helps create the needed loops and folds in the protein molecules. Native and nonnative disulfide cross-links are transiently formed; both correct and incorrect disulfide links can easily form and break. Stability is usually achieved only when the total system is folded. Correct folding also requires guidance, for which continuous oxidoreductase activity helps to ensure that these covalent disulfide links remain flexible until the complete correct folding has been completed.

Redox Regulation

A sensitive chemical balance must be maintained between reducing and oxidizing (redox) conditions along the protein's pathway throughout the entire folding process. The redox gradient between the ER and the cytosol is important for many reasons including intercompartmental signaling. Redox regulation is particularly important in the cell's

> integrated response to oxidative stress, in which adaptive responses emanating from different compartments are coordinated. And redox reactions with opposite electron fluxes must take place in the ER to mediate formation, isomerization and reduction of disulphides. The wealth of redox assistants allows these fluxes to be separate, and channels electron transport through specific protein–protein interactions (Sitia and Braakman, 2003, p. 892).

Emergency Response

At least two examples exist of the cell's complex rapid-response traffic control teams: "[1.] The accumulation of aberrant proteins in the cytosol triggers the heat-shock response, resulting in *de novo* synthesis of hsp70 and other cytosolic chaperones. [2.] But if aberrant proteins accumulate in the ER, cells activate a different response, the Unfolded Protein Response (UPR)" that results in the coordinated synthesis of both specific ER-resident chaperones and enzymes (Sitia and Braakman, 2003, p. 893, brackets added).

A variety of signals can lead to the UPR pathway (Obeng and Boise, 2005). How the diverse unfolded (or misfolded) proteins that accumulate in the ER provoke the UPR pathway is complex. Sitia and Braakman explain that the UPR is a multifaceted system that regulates both the proteins involved in quality control and many other aspects of the entire secretory pathway system (Sitia and Braakman, 2003).

Consequences of Failure

When the system becomes swamped by having too few of the needed structural components, or when it is sent defective parts, ER stress can result, a condition in which the folding ER machinery cannot cope with its protein load (Wickner, et al., 1999). Stress can also be caused by synthesis of mutated or orphan proteins, or the absence of the required cofactors. An example of the latter is scurvy, in which collagen cannot fold properly because of a lack of vitamin C. In an attempt to produce a needed protein, higher levels of the relevant signal are sent because mutated proteins that do not function are unable to provide the feedback needed to stop the signals. As a result, a drastic increase in defective or nonfunctional proteins takes place.

Meltdown Regulation

When damage is so great that further operation of the cell could be lethal to the organism, three independent controls insure that an orderly slowdown occur to try to prevent cell death. These controls are the ER sensors, Ire1, and PERK plus ATF6, which together

> guarantee a tripartite response with synergic strategies. By phosphorylating eIF2alpha, PERK transiently attenuates translation [stops protein synthesis], limiting protein load. ATF6 drives the transcriptional upregulation of many ER-resident proteins and folding assistants [these proteins help to direct the orderly cell shutdown]. Ire1 activates XBP-1, which in turn induces transcription of factors that facilitate ER-associated degradation (ERAD) [this causes the destruction of the ER system itself]. The two-step activation of XBP-1 (transcriptionally induced by ATF6 and post-transcriptionally regulated by Ire1) guarantees the proper timing of the UPR [unfolded protein response]; attempts to fold proteins precede the decision to degrade them [the cell tries to fold them, and if this fails, only then do they break them down for destruction]. If the response fails to clear the ER, apoptosis [cell death] is induced through several pathways (Sitia and Braakman, 2003, p. 893, brackets added).

Mutations and Folding

When a protein is not folded properly, even after repeated attempts, specialized proteins exist to ensure its proper dismantling and recycling (Goldberg,

2003). A mutant or unbalanced subunit that adversely affects proper folding or assembly, triggers this process. These proteins, and all terminally misfolded molecules, are "retrotranslocated" or "dislocated" across the ER membrane "to be degraded by cytosolic proteosomes" (Sitia and Braakman, 2003, p. 892). The proteosomes are complex barrel-shaped macromolecules designed to break down improperly folded proteins and recycle their usable parts (Chin, 2000). Not only are most abnormal, incompletely synthesized, or incompletely assembled proteins degraded, but even incorrectly distributed proteins also are degraded by adenosine triphosphate dependent proteases (Wickner, et al., 1999). How misfolded proteins are recognized and selectively degraded is just beginning to be understood. We do know that it is a very intricate process (Goldberg, 2003).

These quality control mechanisms all must be tightly regulated and serious consequences result from loss of this regulation.

> Quality control must be a balance between retaining and degrading potentially harmful products and not preventing export of biologically active proteins. CFTR mutants in cystic fibrosis illustrate an overzealous quality control, where biologically active mutants cannot leave the ER. In this case, relaxing the quality control could cure the patient. But disease can also originate from defective degradation. If the rate of synthesis of a protein exceeds the combined rates of folding and degradation, a fraction of it will accumulate intracellularly (Sitia and Braakman, 2003, p. 893).

Misfolded proteins must move across the ER membrane rapidly enough and be degraded fast enough by the proteosome to prevent aggregations (called aggresomes) from building up inside (or outside) of the ER. The importance of this process is illustrated by what results if the system does not work properly; "ER storage diseases" are examples. Much has now been "learned about how

Table 1. The Cell's Quality Control System. Most of the Quality Control Systems Reduce the Number of Mutations.

	Step	Requirements
1.	**Proper Protein Processing:**	monitors, transporters, and feedback systems
	Quality Control Features:	inspectors, security guards, and emergency technicians
2.	**Protein Folding:**	chaperones and other protein folding machinery
	Quality Control Features:	checking systems, correct folding recognition system
3.	**Workforce Regulation:**	chaperone number control system
	Quality Control Features:	feedback systems to control up-down regulation system,
4.	**Location Specificity:**	systems to regulate levels of specific protein in specific locations
	Quality Control Features:	feedback systems, up-down regulation systems, such as the fail-safe inspection system.
5.	**Recycling:**	time limit systems to regulate protein-folding progress
	Quality Control Features:	quality and damage monitoring and repair systems.
6.	**Emergency Response:**	heat-shock systems, refolding protein response pathway
	Quality Control Features:	pathway regulation systems
7.	**Meltdown Regulation:**	three independent systems designed to produce an orderly slowdown of protein production
	Quality Control Features:	tightly regulated quality control and systems to regulate the three slowdown protein regulation systems

proteins are handled by the ER folding and quality-control machineries, and some of this knowledge has begun to be translated to industry and to the clinic. Yet, many questions remain" (Sitia and Braakman, 2003, p. 894).

Further elucidation of these detailed, coordinated systems will allow drug designers to produce compounds that respond to deal with faulty elements that cause degenerative diseases, or even to induce apoptosis in tumors, causing them to self-destruct. Although much is known about the mechanisms already described, much remains to be learned about this cell quality control system (Houry et al., 1999).

Summary

Most mutations that cause conformational changes in proteins would have a difficult time making it past the cellular quality control system and, even when they do, the consequences could be catastrophic (Strauss, 1997). Conversely, some mutations may be silent (not expressed) as a result of the actions of some of the quality control mechanisms discussed above (for a discussion of silent mutations, see Brown, 1999). A major concern for neo-Darwinism is how a potentially beneficial mutation could get past the control system without triggering the cell-death alarm. This topic has been largely ignored by Darwinists. Sitia and Braakman (2003) mention evolution only twice, and then only in passing. In both cases, they merely assume the validity of evolution, rather than trying to support or even explain it. They are actually arguing against evolution when they admit that the complex cellular control system described in their paper strongly works against mutational change, and they note that "a certain degree of freedom from quality control is essential for the evolution of proteins" (Sitia and Braakman, 2003, p. 892). If it works too well, macroevolution stops.

The authors admit that this freedom from control comes at a price for multicellular organisms and they give the example of proteins that can take on more than one conformation, but this causes systemic amyloidosis (runaway misfolding, which causes clumping), and can undergo uncontrolled aggregation outside of the cells (Sitia and Braakman, 2003). The evidence we have now indicates that very little freedom exists, severely limiting evolution by mutation. For a summary of the quality control systems discussed in this paper see Table 1.

All living cells are incomprehensibly complex. All the activities discussed above are now going on in every single living cell in your body, and in this review I have only briefly outlined the wonder and complexity of one quality control system. I ignored many other regulation systems such as those regulating development, an important new research area involving genes such as the *hox* genes (see Brown, 2000). No human enterprise comes close to the choreography and efficiency of so many intricately coordinated parts. This surely is a clear example of irreducible complexity (Behe, 1996). If past experience holds true, the cell's quality control factory will prove to be even far more detailed than revealed here (Bergman and You, 1998). This evidence supports the origin of life by direct and miraculous creation and works against neo-Darwinian speculations.

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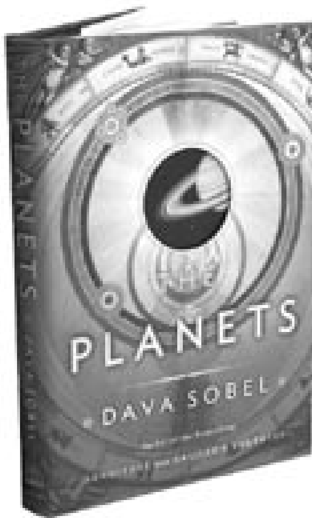

Book Review

The Planets

by Dava Sobel

Viking Penguin Group, New York, 2005, 270 pages, $25.00.

Author Sobel is a former *New York Times* science reporter. She has a gift for expressing science concepts in clear, refreshing style. Her other best sellers include *Longitude* (1995) and *Galileo's Daughter* (2005). Sobel shows a familiarity with scripture. She refers to the Bible in a positive, non-disparaging way, even though she mixes in secular science ideas such as the big bang. I was surprised to see the following quotes in this popular book. The earth will eventually become a "charred cinder where God once walked among men. This dim future, however, lies far ahead as to allow the descendents of Adam and Noah ample time to find another home" (p. 19). Solar eclipses are suggested to be "part of a divine design" (p. 27). Also, page 20 quotes Genesis 1:21–24 regarding the creation of whales and beasts of the earth. It should be added that Sobel also adds detailed astrology ideas to the book without negative comment.

The book surveys historical and modern discoveries within the solar system, and there is poetry in Sobel's writing style. As one example she describes the moon as waxing, waning, and whining for our attention (p. 104). The 15 mile (24 km) height of the Olympus Mons volcano on Mars is pictured as the Alps positioned atop the Rockies, in turn sitting atop the Himalayas (p. 125). The writing is current and includes the 2003 discovery of the planetoid Sedna, slightly larger than Pluto and the most distant known solar system object.

The author includes many minor facts which add to the book's interest. Hence the element uranium, found in 1789, is named in honor of planet Uranus, discovered eight years earlier by William Herschel (p. 184). William had the habit of rubbing onion on his skin to ward off disease while he observed the heavens in the damp night air (p. 204). The book has many further ideas to offer, both trivial and fundamental. A comprehensive glossary and index are included.

Don B. DeYoung
DBDeYoung@Grace.edu