Editor’s Introduction

Quality control in an unreliable world

by Pernille Rørth, Executive Editor of The EMBO Journal and Senior Principal Investigator, Temasek Life Sciences Laboratory (TLL), Singapore
E-mail: p.roth@embojournal.org

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Reviews on quality control: maintenance of molecular and cellular integrity

A cell and its world of molecular machines and organelles is complex—and imperfect, full of small errors and looming catastrophes. It is challenged by stresses, environmental insults and general entropy, but works remarkably well. One reason for this is the existence of quality control. Quality control acts at the level of the important macromolecules, proteins, RNA and DNA, as well as at the organelle and whole-cell level. It serves to edit mistakes and generally maintain functionality. Biological processes are allowed to be a bit messy and slightly unreliable as long as quality control exists.

This focus in The EMBO Journal presents eight reviews, which relate to quality control in molecular and cellular biology. Some reviews are directly about quality control mechanisms, while others are more tangentially connected to it. Some of the processes discussed are clearly appreciated as ‘quality control’ and the term is frequently used, for example in ER quality control. Other quality control processes have other names, but they have in common that they serve to check for correctness and functionality of already produced macromolecules or organelles.

For the quite diverse types of quality control, there are general questions that allow some comparison. First, what is being detected? Does the cell detect the healthy and correct molecule/complex/organelle and allow its persistence? Or is the unhealthy and incorrect version detected and removed? This dichotomy is related to whether degradation or persistence is the default behavior. Second, how is correctness versus incorrectness detected? Is it qualitatively or quantitatively different? Third, how are the mistakes dealt with? Are they corrected/remodeled or are they removed/degraded? And finally, what happens if quality control does not function well? Several of the reviews explore the relationship between quality control and human disease conditions.

The purpose of bringing together reviews from experts in seemingly unrelated areas, is several fold: to give examples of how quality control works and how it is analyzed, at different levels; to allow the reader to explore parallels and differences between the quality control mechanisms and to see whether there are general issues and trends emerging. As quality control is a broad topic, it cannot be comprehensively covered in a small set of reviews. We apologize, in advance, for areas not covered.

Reviews related to protein quality control

The initial set of four reviews is concerned with quality control of proteins and organelles. Although these reviews differ greatly in perspective, they have points of convergence in monitoring the correct conformations of proteins.

The review by Tatsuta and Langer focuses on mitochondria, the cellular engines. Quality control at multiple levels is used to maintain a functional organelle, despite ROS production and other challenges. The intriguing dynamics of mitochondria (fusion and fission) can contribute to quality control of the organelle, and is finely regulated. Mitochondrial dynamics may also link to another clearance pathway, destruction by mitophagy (autophagy of mitochondria). By being intimately connected to apoptosis, mitochondrial quality control brings together the molecular and cellular aspects of quality control.

Whereas mitochondria must cope with the consequences of respiration, the secretory pathway has other challenges, as discussed in the review by Anelli and Sitia. It produces proteins and protein conjugates for export, as well as proteins that are only partially in the external environment. Such proteins must be prepared for the external milieu, and the secretory system has multilevel checking systems to ensure that proteins are properly formatted for this. Aspects of ER quality control, in particular unfolded protein response (UPR) and the clearance pathway know as ERAD (ER-associated degradation), are well studied and many interesting features have been uncovered.

As discussed in the review by Liberek, Lewandowska and Zietkiewicz, even normal cytoplasmic proteins live life on the edge: as a consequence of their conformational plasticity, they can and will misfold on occasion. In the concentrated cellular environment, misfolding can lead to protein aggregation. The review focuses on the role of different types of chaperone proteins in helping cytoplasmic proteins to fold correctly, and in helping to clear up the mess when it goes wrong. Apparently, most proteins need some folding help at some time or another. This essential help system is then boosted when cells are stressed.

The last review of this set, by Winklhofer, Tatzelt and Haass, focuses on diseases associated with protein misfolding and lack of proper quality control or clearance. These are neurodegenerative disease, including Alzheimer’s and Parkinson’s diseases, as well as the infectious prion disease, the latter being particularly fascinating from the point of view of protein folding. The authors discuss for each case the evidence that the diseases are directly caused by misfolding and aggregation of proteins.
proteins. They also consider to what extent phenotypes may be attributed to gain-of-function toxic effects of aggregates versus loss-of-function effects due to protein inactivation.

**Reviews on quality control of DNA and RNA**

Other biological macromolecules are also subject to quality control and this is explored in the second set of reviews dealing with RNA and DNA.

The review by Shyu, Wilkinson and van Hoof discusses the mechanisms of mRNA quality control, specifically nonsense-mediated decay (NMD). By checking whether the stop codon is in the right place in an mRNA, NMD can pick up errors in splicing, as well as some point mutations. The review also explores the relationship of NMD to other types of mRNA regulation feeding into the ‘translate or degrade’ decision, such as that mediated by microRNAs. Much of this regulation uses the 3' UTR of mRNAs as a platform.

The end of the mRNA is the focus of the review by Danckwardt, Hentze and Kulozik, specifically, this review discusses the generation of appropriate 3' ends of mRNAs, as well as diseases associated with misregulation of this step in gene expression. Although not strictly speaking a quality control mechanism, making the right end of the mRNA and of the 3' UTR allows the quality control discussed in the previous review.

The final two reviews deal with DNA, which as a long-term carrier of genetic information is a very well maintained molecule. The review by Kanaar, Wyman and Rothstein discusses how cells deal with DNA ends. Normal chromosome ends need to be distinguished from breakage-induced ends. Also, accidentally induced single- or double-stranded DNA breaks need to be rejoined—preferably correctly. Multiple molecular complexes act in a network of processes to ensure this.

The review by Hakem discusses different types of DNA repair, from correcting simple chemical modifications to handling DNA breaks. The review primarily focuses on what is known from disease situations about the dependence of complex organisms on each of the particular pathways. Should the DNA quality control systems sound an alarm, cells give themselves the necessary time to do the repair by delaying the cell cycle, often as part of a checkpoint. Checkpoints are particularly well-defined quality control posts, for the cell as well as for the scientist.

**Commonalities and contrasts in quality control**

The concerns related to staying functional differ for different macromolecules/organelles. Do they need to be perfect, just OK for a while, or just not be deleterious? What are the time constraints? Misfolding can quickly lead to protein aggregation at any time, whereas DNA must be repaired before onset of a specific transition in the cell cycle. Correspondingly, the quality control mechanisms differ substantially in both logic and details, but parallels may exist when considering each of the general questions posed initially.

**What is detected and how?**

Generally, there is limited evidence that quality control is performed by actively detecting the correct forms. Rather, mistakes or aberrant forms appear to be detected. This is very obvious for proteins. For the mRNA quality control called NMD, detecting a wrong/premature stop and removing the mRNA is a widely accepted model. But the alternative, detecting the right stop and allowing mRNA translation, is also considered in the review by Shyu et al. In DNA end repair, correct forms may be actively detected as productive intermediates in the actual repair process. For any type of quality control, detection of the right form could be advantageous if there is a bottleneck in a process and a well-defined correct form. Perhaps it is more difficult to uncover experimentally and therefore less appreciated. Detecting mistakes is practical as it puts the detector in the right place to start the clearance process or at least mark the problem spot. This mode has the general difficulty that many different—and possibly unpredictable—mistakes or problems have to be recognized. But the quality control systems have some ways of simplifying this.

Mistakes may be detectable by general rather than specific features. For proteins, incorrect folding, and in particular aggregation-prone incorrect folding, is generally reflected in exposure of hydrophobic residues. For DNA, quite dissimilar mismatches due to replication errors or damaged nucleotides can be detected by one mismatch repair complex (MutS), possibly because of common features of most mismatches.

Timers may be used as part of a detection mechanism in quality control. The time that a protein interacts with a particular chaperone, whether in the ER or cytoplasm, could be a measure of whether it is foldable or hopelessly wrong. Similarly, a general mechanism for detection of DNA mismatches compared with matches could also be the kinetics of interaction with MutS complexes. Timing is also discussed as a possible measure of right versus wrong translation stop sites on an mRNA. If an ordered sequence of events normally occurs for the macromolecule, there may be an appropriate timing that can be monitored as an indicator of normal progression.

**What is done about it?**

Once an error or damage has been detected, does the cell attempt to repair or mark the structure for destruction? For proteins, there appears to be a strong contribution of aggregation and refolding. Perhaps this reflects that the battle against misfolding is constant. In addition, stress can suddenly overload the system and cells are not well set up for remaking everything from scratch. Eroneous RNAs of a cell may generally be destined for the trash, with little emphasis on repair. This is at least the case when considering sequence errors—folding is harder to analyze. DNA molecules generally do not have the option of simple degradation, but must instead be repaired if damaged. Some types of repair, however, involve a significant element of destruction before remaking. For example, pieces of DNA around a point of damage may be recessed and the whole section resynthesized. Sections of mitochondria may bud off and be degraded, leaving the main structure intact. In this case, molecular and organellar dynamics may allow concentration of damaged molecules before the destructive step, a cost-effective approach.

The choice of repair versus destruction may not be general for one type of quality control, but depends on the error and the costs. In the context of protein folding, this is considered explicitly by Liberek et al: what is the energetic cost of...
destruction versus repair/refolding, and what is most advantageous to the cell? But how much does a cell care about energetic cost? The latter will likely reflect evolutionary pressures: does the individual cell (bacterium, fungus, algae) have to survive and multiply with limited resources? Or does it generally have plenty of resources but mistakes might be paid for dearly (mammalian germ cells, neurons)? The choice of repair versus destruction may also simply reflect what is possible in the relevant timeframe. Some systems will attempt refolding/repair and move to destructive clearance only if this fails. A secondary quality control timer may be employed to induce the switch from repair to destruction.

**Turnover is key**

Production and elimination ensure cellular homeostasis, whether for biological macromolecules (production and degradation) cell (growth and death) or organelles (biogenesis and autophagy). Active turnover seems to be the rule rather than the exception. One useful feature of turnover is that it provides multiple mechanisms for adapting to new circumstances. Another very useful feature is that it allows for quality control to be integrated naturally and continuously. Macromolecules rarely come with time-stamps so it is not a priori easy to remove the old and tired versions by automatic clearance. Integrating some sort of quality control makes good sense.

The reverse may also occur: interactions designed for quality control may be employed as regulatory mechanisms controlling the efficiency of specific outputs, for quantitative regulation. One example is the many roles of chaperone proteins. Intriguing also is the integration of mitochondrial quality control into control of cell survival. Even the NMD mechanism may be used as a quantitative regulatory device.

Finally, as discussed in the review by Kanaar et al, dynamics and turnover of interactions within repair machineries may be an integral part of the quality control mechanism. The balance of multiple reversible processes, each with some selectivity, may ensure the overall robustness and fidelity. Generally, well-regulated production machineries seem to be matched by equally elaborate degradation and quality control mechanisms.

**Molecular quality control, cellular quality control and disease**

The reviews of this focus discuss quality control at the molecular and sub-cellular level. For multicellular organisms quality control is also important at the tissue level, with failures to pass often causing cells to undergo apoptosis. We have not included reviews on this topic, largely because of the many reviews of apoptosis already in the literature. But clearly some of the quality control issues discussed above apply in this context as well. For example, does the surveillance system detect the correct features (correct for the particular environment) or mistakes? What determines the type of response? Can the cell be fixed (by outside input) or will mistakes lead to destruction/cell death? The answers will likely depend on which cell is being analyzed—and what methods are available for analysis.

By monitoring the quality of templates as well as products (DNA, RNA and protein), of molecules as well as organelles and cells, nature has set up a system of quality control cross-checks that probably catches most mistakes—but not all. In the discussion of protein or organellar quality control, it is noted that malfunction may lead to neurodegenerative diseases. A neural bias makes sense, as a well-connected neuron should be functional for a long time, whereas many other cell types are eliminated when defective, or even as a matter of course. Therefore, proper housekeeping within each cell is an essential attribute for a well-functioning brain. As proteins and RNA are constantly produced and possibly altered, their quality control must be ever-vigilant. DNA quality control is different; its mistakes mostly manifest themselves when cells divide. Mistakes that are not caught at the molecular level, may be caught at the next cellular/tissue level and lead to cell apoptosis. Mistakes slipping by both quality control levels may ultimately cause tumors.

**Quality control and evolution**

As an integrated and important aspect of multiple biological processes, molecular quality control is also connected to evolution. As discussed above, evolutionary concerns may bias the mode of quality control. But quality control mechanisms may also affect evolution.

A change in DNA sequence triggered by the absence of repair, or imperfect repair, is one relatively straightforward example. It is tempting to speculate that quality control works as well as needed, but a certain degree of error is tolerated in the long run to provide diversity. An extreme version of this error-prone approach is seen in the generation of diversity in cells of the adaptive immune system, which may also involve deliberate ‘misuse’ of DNA quality control systems. And while DNA generally seems designed for stability, it is interesting that many species chose to methylate cytosines in their DNA as part of chromatin regulatory mechanisms, given the possibility of deamination of 5-methylcytosine to thymidine and thus, after mismatch repair or replication, potential DNA sequence changes.

The connection between protein quality control and evolution may also be quite significant—although less obvious. Chaperones, or specifically Hsp90 proteins, have been argued to enhance genetic variance and thus act as ‘capacitors’ of evolution. This has also been experimentally explored in flies, plants and fungi by the Lindquist laboratory. The rationale is that Hsp90 normally buffers modest genetic variation by helping to fold or eliminate altered proteins, allowing variants to accumulate silently in the genome. Phenotypic consequences of the variants may then be manifest under stress, providing a chance for further selection if effects are positive. Generally non-DNA quality control may, by correcting unstable or imperfect forms, allow more variability and flexibility and thus provide fertile ground for evolution.

We hope the readers will enjoy this focus on quality control. From *The EMBO Journal*, we thank the authors of the reviews for their contributions, reviews that are interesting in their own right and that may also inspire new ideas and connections in the context of the focus.