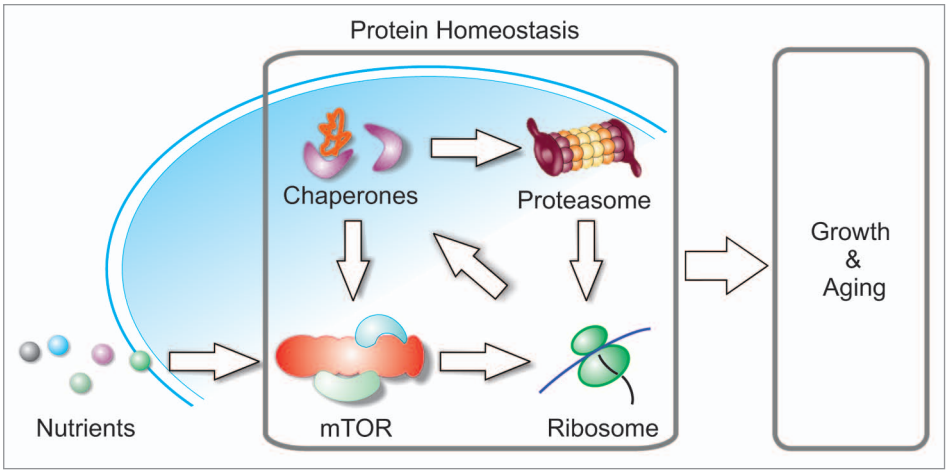

Figure 3. The interface between chaperone-mediated stress response and mTOR-mediated nutrient-sensing system serves as a central homeostatic mechanism. Dysregulation of both pathways has been implicated in aging and age-associated diseases.

promote proper protein folding, the successful folding process of newly synthesized polypeptides primarily depends on the fidelity of transcription and translation. Proteins mistranslated should not be subject to chaperone rescue and are efficiently identified by degradation systems.[81] This translational challenge is illustrated by observations that even under optimal conditions, nearly 10% of newly synthesized proteins are mistranslated,[82] and 20–30% of all nascent polypeptides are rapidly degraded owing to folding errors.[83] Previous studies have concentrated on how changes of mTORC1 signaling lead to alteration of ribosome biogenesis and mRNA translation initiation.[84] Less attention has focused on how alterations of translation speed (elongation rate) may influence the translation fidelity. As discussed above, our recent studies have begun to reveal the interconnection between the mTORC1 signaling pathway and the chaperone network, which affects the co-translational folding of nascent polypeptides. However, it remains possible that mTORC1-controlled elongation may directly influence the accuracy of amino acid incorporation.

mTORC1 regulates protein translation at multiple stages, including initiation and elongation. Although the regulatory mechanisms impinging on the initiation steps have received considerable attention, accumulating information points to the elongation phase as a target for control under defined circumstances. Most of the recent advances relate to the regulation of eEF2 and its cognate kinase eEF2 kinase. eEF2 mediates the translocation step of elongation where the ribosome moves relative to the mRNA by one codon and the peptidyl-tRNA shifts from the A site to the P site. eEF2 undergoes phosphorylation at Thr56 within the GTP-binding domain and this modification interferes with its ability to bind the ribosome, thus inhibiting its function.[85] mTORC1 negatively regulates eEF2 kinase and thereby activates eEF2. The multiplicity of regulatory inputs into the enzyme that phosphorylates eEF2 suggests that it has a key role in cellular regulation, in particular the overall control of protein synthesis.[86]

Increasing evidence has supported the notion that the local discontinuous translation (ribosome pausing) temporally separates the translation of segments of the peptide chain and actively coordinates their co-translational folding.[87] An interesting recent report indicated that slowing bacterial translation speed enhances eukaryotic protein folding efficiency.[88] We have observed that, in cells with hyperactive mTORC1 signaling, the increased elongation speed is accompanied with the deficiency of luciferase folding. Importantly, slowing down translation elongation by rapamycin treatment increases the folding efficiency (unpublished results). Several possibilities could contribute to the inverse correlation between elongation speed and folding quality of nascent polypeptides. First, the higher protein production could exceed the chaperone availability, thereby reducing the overall co-translational folding capacity. Second, the faster translation speed may eliminate the ribosome pausing necessary for co-translational folding. Third, the increased elongation rate potentially compromises the translational fidelity by promoting mis-incorporation of amino acids. mRNA translation is the most error-prone step in gene expression as approximately 3 codons in 10,000 are mistranslated.[82] Therefore, it is conceivable that the increased translation speed under hyperactive mTOR signaling generates more error proteins. Given the fact that the most common molecular signal of aging is an accumulation of altered proteins derived from both erroneous biosynthesis and post-synthetic modification, one of the future challenges will be to elucidate how mTOR-controlled translational regulation influences the translation fidelity as well as the folding process of translational products.

Conclusions and Outlook

The interface between chaperone-mediated stress response and mTOR-mediated nutrient-sensing system can be viewed as a central homeostatic mechanism (**Fig. 3**). The concept of "less is more" was originally derived from the relationship between mTOR signaling and aging based on the observation in a wide range of organisms that reduced TOR signaling extends lifespan.[15] It is clear that the same concept also applies to the protein homeostasis. Although accumulating evidence has begun to divulge an important cellular surveillance mechanism linking protein quantity and quality control, more questions than answers arise. For example, how does the cell differentiate the physiological fluctuation from severe stresses? What is the physiological switch between cell growth signaling and cell survival pathways? What is the common mechanism for the ribosome acting as a central platform for multiple signaling pathways? These mutual connections may help formulate the

cellular decision between life and death under different conditions. This framework not only offers an excellent opportunity for exploring the biological significance of the link between nutrient signaling and chaperone network, but also provides an array of putative drug targets for slowing down aging and age-associated pathologies, including cancer, diabetes and neurodegenerative disorders.

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