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Redox Regulation in Protein Folding and Chaperone Function

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1. Introduction: Protein Folding, Heat Shock Proteins, Molecular Chaperones

Chaperones are ubiquitous, highly conserved proteins, which utilize a cycle of ATP-driven conformational changes to refold their targets, and which probably played a major role in the molecular evolution of modern enzymes [1,2]. Environmental stress (a sudden change in the cellular environment, to which the cell is not prepared to respond, such as heat shock) leads to the expression of most chaperones, which therefore are called heat-shock, or stress proteins. Lacking a settled view about their action in the molecular level [3], chaperones are still best classified by their molecular weights (Table 1). Besides to promote the formation of the correct conformation of nascent or damaged proteins chaperones also assist in the formation of correct disulfide bridges offering the help protein disulfide isomerases (PDI-s) [4,5].

Higher levels of cellular organization also need a constant remodeling. Chaperones are obvious candidates to provide help in these processes. About twenty years ago based on high-voltage electron microscopy Keith A. Porter and co-workers suggested the existence of a cellular meshwork, called as "microtrabecular lattice" to organize cytoplasmic proteins and RNA-s [6]. Almost instantly a fierce debate arose considering the lattice as an artifact of the techniques used. However, as time passes more and more data provide indirect evidence for a high-order organization of the cytoplasm [7]. Chaperones are ideal candidates for being a major constituent of a cytoplasmic meshwork: they are highly abundant, form a loose and dynamic complex with all the elements of the cytoskeleton and each other, and also attach to a plethora of other proteins. Several lines of initial evidence shows that disruption of chaperone/protein complexes disturbs the organization of cytoplasmic traffic of several proteins, such as the steroid receptors, and accelerates cell lysis [8-10].

2. Redox Chaperones in the Endoplasmic Reticulum and in the Periplasm: Quality Control of Secreted Proteins

Secreted proteins have to prepared for the oxidative millieu of the extracellular space. A rapid oxidation would result in the formation of numerous incorrect disulfide bridges, which would lock the protein in a distorted conformation. Therefore folding of secreted/plasma membrane proteins is most probably accompanied by their *gradual* oxidation in the endoplasmic reticulum (ER). This would imply the existence of a redox gradient along the secretory

pathway. The first tools, such as the redox sensitive green fluorescent protein (GFP, which, in fact, has a yellow colour in this case, 11) to measure this putative gradient have already been established.

Table 1. Major classes of molecular chaperones

Most important eukaryotic representatives	Reviews
small heat shock proteins (e.g. Hsp27)	21
Hsp60	1, 46
Hsp70 (Hsc70 , Grp78)	1, 46
Hsp90	8, 47
Hsp104	18
Peptidyl-prolyl *cis/trans*-isomerases	39
Protein disulfide isomerases	4,5

Co-chaperones (chaperones which help the function of other chaperones listed) were not included in this table, albeit almost all of these proteins also possess a "traditional" chaperone activity in their own right. Several chaperones of the endoplasmic reticulum (e.g. calreticulin, calnexin, etc.), which do not belong to any of the major chaperone families, as well as some heat shock proteins (e.g. ubiquitin), which do not possess chaperone activity were also not mentioned.

The abbreviation "Hsp" and "Grp" refer to heat shock proteins, and glucose regulated proteins, chaperones induced by heat shock or glucose deprivation, respectively. Numbers refer to their molecular weight in kDa.

Hsc70 denotes the cognate (constitutively expressed) 70 kDa heat shock protein homologue in the cytoplasm.

Another mechanism for the control of gradual oxidation is the reorganization of rapidly formed, incorrect disulfide bonds. This is performed by the numerous protein disulfide isomerases (PDI-s). These proteins have been discovered independently by the group of Christian Anfinsen [12], and by Pal Venetianer and Bruno Straub [13] in Hungary almost fourty years ago. In the meantime the existence of a large number of the family has been uncovered, such as Erp29, Erp57, Erp59, Erp72 and others. The exact substrate specificity of these enzymes is not known. However, Erp59 seems to be the most abundant member of the family and Erp72 acts mainly on glycosylated proteins. The formation of disulfide bridges requires the accessibility and correct positioning of SH groups. This is achieved by the "conventional" chaperone activity of protein disulfide isomerases [14] as well as by their cooperation with other chaperones, such as Grp78 in the ER [15]. The correct chaperone/target ratio is very important in the action of PDI-s. In case of a large excess of targets PDI acts as an "anti-chaperone" promoting inter- and not intramolecular disulfide bridge formation [16]. Therefore, in case of ER-overload or after the poisoning by reducing agents PDI-s may promote the formation of covalently linked aggregates instead of their usual role as redox-chaperones.

Besides the reorganization of incorrect disulfide bridges protein disulfide isomerases also participate in the direct oxidation of secreted proteins. In these cases oxidized protein disulfide isomerases are reduced by the ER transmembrane proteins Ero1-L-alpha and Ero1-L-beta requiring flavin adenine dinucleotide as a cofactor. The two Ero-s seem to act on

different PDI-s, and the more active form, Ero1-L-beta is overregulated if the ER experiences an excess of unfolded proteins [17]. In contrast of yeast PDI, which is present predominantly in the oxidized state, most mammalian PDI-s are partially reduced. The small pool of oxidized PDI suggests that in mammalian cells oxidative equivalents are rapidly transferred to cargo proteins [17] or the redox gradient along the secretory pathway is more expressed than in yeast.

Protein disulfide isomerases are not always ER-resident proteins. They are also secreted to the extracellular medium, where they continue their folding assistance, and prevent the formation of extracellular protein aggregates [18,19]. In the *E. coli* periplasm a slightly different mechanism controls the oxidation of proteins to that of the ER: oxidation is achieved by a separate arm of proteins involving DsbA, which is reoxidized by the inner membrane protein DsbB. The *E. coli* protein disulfide isomerases are DsbC and DsbG, which are reoxidized by the membrane protein DsbD [4,5].

Table 2. Cytoplasmic redox chaperones

Chaperone	Function	References
small heat shock proteins (Hsp25, Hsp27)	increases reduced glutathione levels by increased glucose-6-phosphate dehydrogenase, glutathione reductase and glutathione transferase activities	20,21
Hsp32'	heme oxygenase-1, an important component of oxidative stress-mediated cell injury	22
Hsp33	oxidation-activated chaperone in yeast	23
Hsp70	has (probably indirect) anti-oxidant properties	50
cytochrome c	released from mitochondria in apoptosis, chaperone function has been detected	27
thioredoxin'	promotes cytoplasmic oxidation of selected proteins	24
ERV1/ALR'	promotes the cytoplasmic formation of disulfide bridges	25
MsrA and MsrB'	methionine sulfoxide reductase: regenerates functional methionine	26

'No direct chaperone activity has been demonstrated yet.

3. Redox Chaperones in the Cytoplasm: Another Defense against Oxidative Damage

From the traditional chaperones (Table 1) the small heat shock proteins and Hsp70 act as cytoplasmic "antioxidants" (Table 2). Small heat shock proteins elevate reduced glutathione levels by promoting an increase in glucose-6-phosphate dehydrogenase activity and by a somewhat smaller activation of glutathione reductase and glutathione transferase [20,21]. Heme oxygenase a heat shock protein responsible for the production of the antioxidants

biliverdin and bilirubin is an important component of cellular defense mechanisms against oxidative stress [22]. Yeast cells contain a rather unique chaperone, Hsp33, which is activated after oxidative stress [23]. SH-groups of some specific proteins (such as the glucocorticoid receptor) are maintained in the reduced state or just inversely: oxidized by thioredoxins in the cytoplasm [24]. In turn, these proteins are most probably oxidized by members of the ERV1/ALR protein family [25]. Oxidized methionines are reduced by special enzymes, the methionine-sulfoxide reductases [26]. An interesting member of redox cytoplasmic chaperones is cytochrome c, which is only a 'guest' in the cytoplasm during its apoptotic release from mitochondria and has been established as a chaperone a long time ago [27].

4. Redox Control of Chaperone Induction

Oxidative stress leads to a massive induction of heat shock proteins. This is partly mediated by the oxidation-induced formation of damaged proteins [28], which occupy chaperone-binding sites, and liberate heat shock factor 1 (HSF1), the transcription factor responsible for Hsp induction [29]. However, a decrease in reduced glutathione levels (by oxidation or by the formation of S-nitroso-glutathione by NO) [30] may also lead to a direct activation of HSF1 [31]. Interestingly, a more reduced cellular environment also helps chaperone induction [32]. In agreement with this, heat shock itself leads to a rapid elevation of reduced glutathione [33]. On the other hand, millimolar concentration of a reducing agent impairs the activation of HSF1 [34].

5. Redox Regulation of Chaperone Function

Cytoplasmic chaperones, such as small heat shock proteins, or Hsp90 usually loose their activity after the oxidation of their cysteine or methionine residues [35,36]. Both in Hsp70 and Hsp90 the oxidation-prone cysteine is in the close vicinity of an ATP binding site [36,37], which may explain the rapid loss of their chaperone activity after oxidation. Small heat shock proteins were recently established as ATP-binding chaperones, therefore the above explanation may have a more general implication than we previously thought. Chaperone-inactivation may also occur by S-nitrosylation after NO, or peroxonitrite addition. On the contrary to this general trend, the yeast cytoplasmic chaperone, Hsp33 is activated after oxidative stress [23]. Though its homologues have not been found in higher eukaryotes, a similar mechanism would be very logical to operate in other cells. Rapoport and co-workers [38] raised the interesting possibility that oxidation of PDI may trigger a release of its substrate, which would then travel further in the secretory chain or, as in the case of cholera toxin, would be a subject of a retrograde transport back to the cytoplasm.

6. Changes of Chaperones and Redox Function in Disease and Aging

In several diseases, such as in endothelial dysfuncton, in diabetes, in Alzheimer and Parkinson diseases the redox homeostasis becomes severly damaged [39,40]. The amount of oxidized proteins increases, which requires a larger amount of chaperones to cope with the conformational damage and leads to chaperone induction. However, chronic stress exhausts the chaperone-induction signalling mechanisms, and damaged proteins begin to accumulate. Moreover, oxidized proteins are much poorer substrates, but highly effective inhibitors of the proteasome [41]. All these changes also occur during ageing with the

concomitant decrease in the chaperone-induction capacity of the aging organism [42]. In contrast, enhanced antioxidant systems (such as the overexpression of Cu-Zn-superoxide dismutase) as well as an increased amount of heat shock proteins leads to longevity [43].
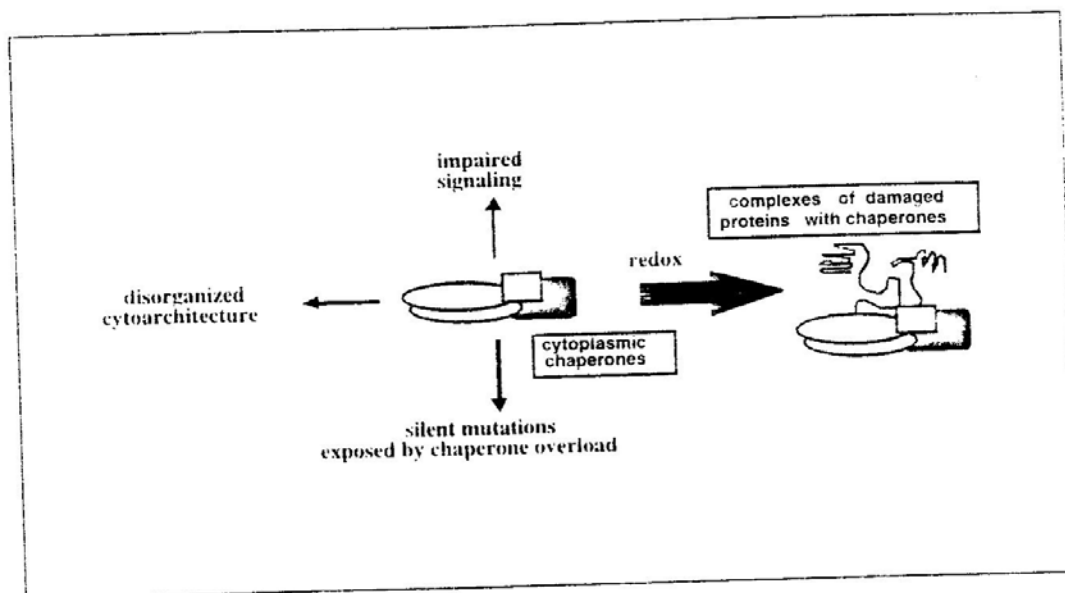

Fig. 1. Chaperones as major transmitters of changes in redox homeostasis to the life of the whole cell. Clockwise from bottom: (a) phenotypically buffered, silent mutations require the assistance of chaperones to rescue them from folding traps [44,45]. (b) Chaperones form low affinity and highly dynamic extensions of the cytoskeleton participating in cellular traffic and in the organisation of the cytoarchitecture [8-10]. (c) Cytoplasmic chaperones of eukaryotic cells participate in the maintenance of the conformation of some, selected protein substrates. Most of these unstable proteins are parts of various signalling cascades [8,47]. (d) After changes in the redox homeostasis, chaperones become more and more occupied by damaged proteins. As a consequence of this: (a) silent mutations escape and contribute to the onset of polygenic diseases; (b) cell architecture becomes disorganised; (c) signalling is impaired. The verification of these – presently largely hypothetical – changes requires further experimentation.

7. Perspectives: Chaperones as Central Players in the Transmission of Redox Changes to the Life of the Cell

Oxidative damage, together with other proteotoxic insults during the propagation of various diseases and ageing results in a change between the ratio between damaged proteins and available chaperone capacity. The chaperone-overload, which is a consequence of these events leads to rather unexpected changes. Recently one of the major cytoplasmic chaperones, Hsp90, was shown to act as posttranslational "silencer" of several genetical changes by assisting in an efficient repair of folding defects [44]. After a large stress transient chaperone-overload prevents the conformational repair of misfolded mutants. Therefore many, previously hidden genotypical changes appear in the phenotype resulting in a "boom" of genetical variations in the whole population. This may help the selection of a beneficial change, which, in turn, may help the adaptation of the population to the changing environmental conditions.

Under stressful conditions most of the exposed mutations are disadvantageous, and tend to disappear from the population by natural selection. According to a recent hypothesis [45] the development of modern medical practice depressed natural selection by its groundbreaking achievements to reduce prenatal and infant mortality leading to a rise of phenotypically silent mutations in the genome. As a consequence we carry more and more

chaperone-buffered, silent mutations from generation to generation. The chance of the phenotypic manifestation of these mutations becomes especially large in aged subjects, where protein damage is abundant, and chaperone induction is impaired. The background of misfolded proteins increases and by competition prevents the chaperone-mediated buffering of silent mutations. Phenotypically exposed mutations contribute to a more abundant manifestation of multigene-diseases, such as atherosclerosis, autoimmune-type diseases, cancer, diabetes, hypertensive cardiovascular disease and several psychiatric illnesses (Alzheimer disease, schizophrenia, etc.). The "chaperone overload" hypothesis emphasises the need for efficient ways to enhance chaperone-capacity in ageing subjects, and calls for the identification and future "repair" of silent mutations [45].

After oxidative damage in the cytoplasm or "reductive damage" in the endoplasmic reticulum, the resulting chaperone overload changes the whole life of the cell. Besides the exposure of the previously hidden mutations signaling becomes impaired and the cellular architecture is disorganized (Figure 1). Chaperones may act as central players of the transmission of redox changes in the life of the cell.

References

1. F.U. Hartl, Molecular chaperones in cellular protein folding. Nature 381 (1996) 571-580.
2. P. Csermely, Proteins, RNA-s, chaperones and enzyme evolution: a folding perspective. Trends in Biochem. Sci. 22 (1997) 147-149.
3. P. Csermely, The "chaperone-percolator" model: a possible molecular mechanism of Anfinsen-cage type chaperone action. BioEssays 21 (1999) 959-965.
4. U. Raina and D. Missiakas, Making and breaking disulfide bonds. Annu. Rev. Microbiol. 51 (1997) 179-202.
5. A. Rietsch and J. Beckwith, The genetics of disulfide bond metabolism. Annu. Rev. Genetics 32 (1998) 163-184.
6. M. Schawa, J. van Blerkom and K.R. Porter, Stabilization of the cytoplasmic ground substance in detergent-opened cells and a structural and biochemical analysis of its composition. Proc. Natl. Acad. Sci. USA 78 (1981) 4329-4333.
7. A.S. Verkman, Solute and macromolecule diffusion in cellular aqueous compartments. Trends in Biochem. Sci. 27 (2002) 27-33.
8. W.B. Pratt, A.M. Silverstein, and M.D. Galigniana, A model for the cytoplasmic trafficking of signalling proteins involving the hsp90-binding immunophilins and p50cdc37. Cellular Signaling 11 (1999) 839-851.
9. P. Csermely, A nonconventional role of molecular chaperones: involvement in the cytoarchitecture. News in Physiol. Sci. 15 (2001) 123-126.
10. A. Pato, K. Mihaly and P. Csermely, Chaperones and cytoarchitecture: geldanamycin induces an accelerated flux of cytoplasmic proteins from detergent-treated cells. Eur. J. Biochem. 268 (2001) 107a.
11. H. Ostergaard, A. Henriksen, F. G. Hansen and J. R. Winther, Shedding light on disulfide bond formation: engineering a redox switch in green fluorescent protein. EMBO J. 20 (2001) 5853-5862.
12. R.F. Goldberger, C.J. Epstein and C.B. Anfinsen, Acceleration of reactivation of reduced bovine pancreatic ribonuclease by a microsomal system from rat liver. J. Biol. Chem. 238 (1963) 628-635.
13. P. Venetianer and F. B. Straub, The enzymic reactivation of reduced ribonuclease. Biochim. Biophys. Acta 67 (1963) 166-167.
14. Y. Yao, Y. Zhou and C. Wang, Both the isomerase and chaperone activities of protein disulfide isomerase are required for the activation of reduced and denatured acidic phospholipase A2. EMBO J. 16 (1997) 651-658.
15. M. Mayer, U. Kies, R. Kammermeyer and J. Buchner, BiP and PDI cooperate in the oxidative folding of antibodies in vitro. J. Biol. Chem. 275 (2000) 29421-29425.
16. A. Puig and H.F. Gilbert, Protein disulfide isomerase exhibits chaperone and anti-chaperone activity in the oxidative refolding of lysozyme. J. Biol. Chem. 269 (1994) 7764-7771.
17. A. Mezghrani, A. Fassio, A. Benham, T. Simmen, I. Braakman and R. Sitia, Manipulation of oxidative protein folding and PDI redox state in mammalian cells. EMBO J. 20 (2001) 6288-6296.
18. H. Takemoto, T. Yoshimori, A. Yamamoto, Y. Miyata, I. Yahara, K. Inoue and Y. Tashiro, Heavy chain binding protein (BiP/grp78) and endoplasmin are exported from the endoplasmic reticulum in rat exocrine pancreatic cells, similar to protein disulfide-isomerase. Arch. Biochem. Biophys. 296 (1992) 129-136.

19. P. Delom, B. Mallet, P. Carayon and P.J. Lejeune, Role of extracellular molecular chaperones in the folding of oxidized proteins. Refolding of colloidal thyroglobulin by protein disulfide isomerase and immunoglobulin heavy chain-binding protein.. J. Biol. Chem. 276 (2001) 21337-21342.

20. A.P. Arrigo, Small stress proteins: Chaperones that act as regulators of intracellular redox state and programmed cell death. Biol. Chem. 379 (1998) 19-26.

21. X. Preville. F. Salvemini, S. Giraud, S. Chaufour, C. Paul, G. Stepien. M.V. Ursini and A.P. Arrigo, Mammalian small stress proteins protect against oxidative stress through their ability to increase glucose-6-phosphate dehydrogenase activity and by maintaining optimal cellular detoxifying machinery. Exp. Cell Res. 247 (1999) 61-78.

22. K.K. Elbirt and H.L. Bonkovsky, Heme oxygenase: Recent advances in understanding its regulation and role. Proc. Assoc. Am. Physicians 111 (1999) 438-447.

23. U. Jakob. W. Muse, M. Eser and J.C. Bardwell. A chaperone activity with a redox switch. Cell 96 (1999) 341-352.

24. K. Okamoto. H. Tanaka, H. Ogawa. Y. Makino. H. Eguchi, S. Hayashi, N. Yoshikawa, L. Poellinger. K. Umesono and I. Makino. Redox dependent regulation of nuclear import of the glucocorticoid receptor. J. Biol. Chem. 274 (1999) 10363-10371.

25. T.G. Senkevich. C.L. White, E.V. Koonin and B. Moss. A viral member of the ERV1/ALR protein family participates in a cytoplasmic pathway of disulfide bond formation. Proc. Natl. Acad. Sci. USA 97 (2000) 12068-12073.

26. R. Grimaud, B. Ezraty, J.K. Mitchell. D. Lafitte, C. Briand, P.J. Derrick and F. Barras, Repair of oxidized proteins. Identification of a new methionine sulfoxide reductase. J. Biol. Chem. 276 (2001) 48915-48920.

27. C.K. Ramakrishna Kurup, T.S. Raman, J. Jayaraman and T. Ramasarma, Oxidative reactivation of reduced ribonuclease. Biochim. Biophys. Acta 93 (1964) 681-683.

28. A.T. McDuffee, G. Senisterra, S. Huntley, J.R. Lepock, K.R. Sekhar, M.J. Meredith, M.J. Borrelli, J.D. Morrow and M.L. Freeman, Proteins containin non-native disulfide bonds generated by oxidative stress can act as signals for the induction of the heat shock response. J. Cell. Physiol. 171 (1997) 143-151.

29. R.I. Morimoto, Regulation of the heat shock transcriptional response: cross talk between a family of heat shock factors, molecular chaperones, and negative regulators. Genes Dev. 12 (1999) 3788-3796.

30. Y.M. Kim, M.E. de Vera, S.C. Watkins and T.R. Billiar, Nitric oxide protects cultured rat hepatocytes from tumor necrosis factor-alpha-induced apoptosis by inducing heat shock protein 70 expression. J. Biol. Chem. 272 (1997) 1402-1411.

31. M.R. Jacquier-Sarlin and B.S. Polla. Dual regulation of heat-shock transcription factor (HSF) activation and DNA-binding activity by H2O2: role of thioredoxin. Biochem. J. 318 (1996) 187-193.

32. K. Kato. H. Ito and K. Okamoto. Modulation of the arsenite-induced expression of stress proteins by reducing agents. Cell Stress Chaperones 2 (1997) 199-209.

33. J.B. Mitchell and A. Russo, Thiols. thiol depletion, and thermosensitivity. Radiat. Res. 95 (1983) 471-485.

34. L.E. Huang, H. Zhang, S.W. Bae and A.Y. Liu, Thiol reducing reagents inhibit the heat shock response. J. Biol. Chem. 269 (1994) 30718-30725.

35. N. Gustavsson, B.P. Kokke, B. Anzelius, W.C. Boelens and C. Sundby, Substitution of coserved methionines by leucines in chloroplast small heat shock protein results in loss of redox response but retained chaperone-like activity. Protein Sci. 10 (2001) 1785-1793.

36. G. Nardai, B. Sass, J. Eber, Gy. Orosz and P. Csermely, Reactive cysteines of the 90 kDa heat shock protein, Hsp90. Arch. Biochem. Biophys. 384 (2000) 59-67.

37. Cs. Sōti, A. Rácz and P. Csermely, A nucleotide-dependent molecular switch controls ATP binding at the C-terminal domain of Hsp90: N-terminal nucleotide binding unmasks a C-terminal binding pocket. J. Biol. Chem. 277 (2002) 7066-7075

38. A. Tsai, C. Rodighiero, W.I. Lencer and T.A. Rapoport, Protein disulfide isomerase acts as a redox-dependent chaperone to unfold cholera toxin. Cell 104 (2001) 937-948.

39. G. Nardai, L. Braun, M. Csala. V. Mile, P. Csermely, A. Benedetti, J. Mandl and G. Banhegyi, Protein disulfide isomerase and protein thiol dependent dehydroascorbate reduction and ascorbate accumulation in the lumen of the endoplasmic reticulum. J. Biol. Chem. 276 (2001) 8825-8828.

40. L.M. Sayre, M.A. Smith and G. Perry, Chemistry and biochemistry of oxidative stress in neurodegenerative disease. Curr. Med. Chem. 8 (2001) 721-738.

41. B. Friguet. E.R. Stadtman and L.I. Szweda, Modification of glucose-6-phosphate dehydrogenase by 4-hydroxy-2-nonenal. Formation of cross-linked protein that inhibits the multicatalytic protease. J. Biol. Chem. 269 (1994) 21639-21643.

42. D.M. Hall, G.L. Sattler, C.A. Sattler, H.J. Zhang, L.W. Oberley, H.C. Pitot and K.C. Kregel, Aging lowers steady-state antioxidant enzyme and stress protein expression in primary hepatocytes. J. Gerontol. 56A (2001) B259-B267.

43. R. Arking, V. Burde, K. Graves, R. Hari, E. Feldman. A. Zeevi, S. Soliman, A. Saraiya, S. Buck, J. Vettraino, K. Sathrasala. N. Wehr and R.L. Levine, Forward and reverse selection for longevity in Drosophila is characterized by alteration of antioxidant gene expression and oxidative damage patterns. Exp. Gerontol. 35 (2000) 167-185.

44. S.L. Rutherford and S. Lindquist, Hsp90 as a capacitor for morphological evolution. Nature 396 (1998) 336-342.

45. P. Csermely. Chaperone-overload as a possible contributor to "civilization diseases": atherosclerosis. cancer. diabetes. Trends in Genetics 17 (2001) 701-704.

46. A. Bukau and A.L. Horwich. The Hsp70 and Hsp60 chaperone machines. Cell 92 (1998) 351-366.

47. P. Csermely. T. Schnaider. Cs. Söti, Z. Prohászka and G. Nardai, The 90 kDa molecular chaperone family: structure. function and clinical applications. A comprehensive review. Pharmacol. Therapeut. 79 (1998) 129-168.

48. J. Porankiewicz, J. Wang and A.K. Clarke. New insights into the ATP-dependent Clp protease: Escherichia coli and beyond. Mol. Microbiol. 32 (1999) 449-458.

49. S.F. Gothel and M.A. Marahiel. Peptidyl-prolyl cis-trans isomerases, a superfamily of ubiquitous folding catalysts. Cell. Mol. Life Sci. 55 (1999) 423-436.

50. Y.M. Kim, M.E. de Vera. S.C. Watkins and T.R. Billiar, Nitric oxide protects cultured rat hepatocytes from tumor necrosis factor-alpha-induced apoptosis by inducing heat shock protein 70 expression. J. Biol. Chem. 272 (1997) 1402-1411.
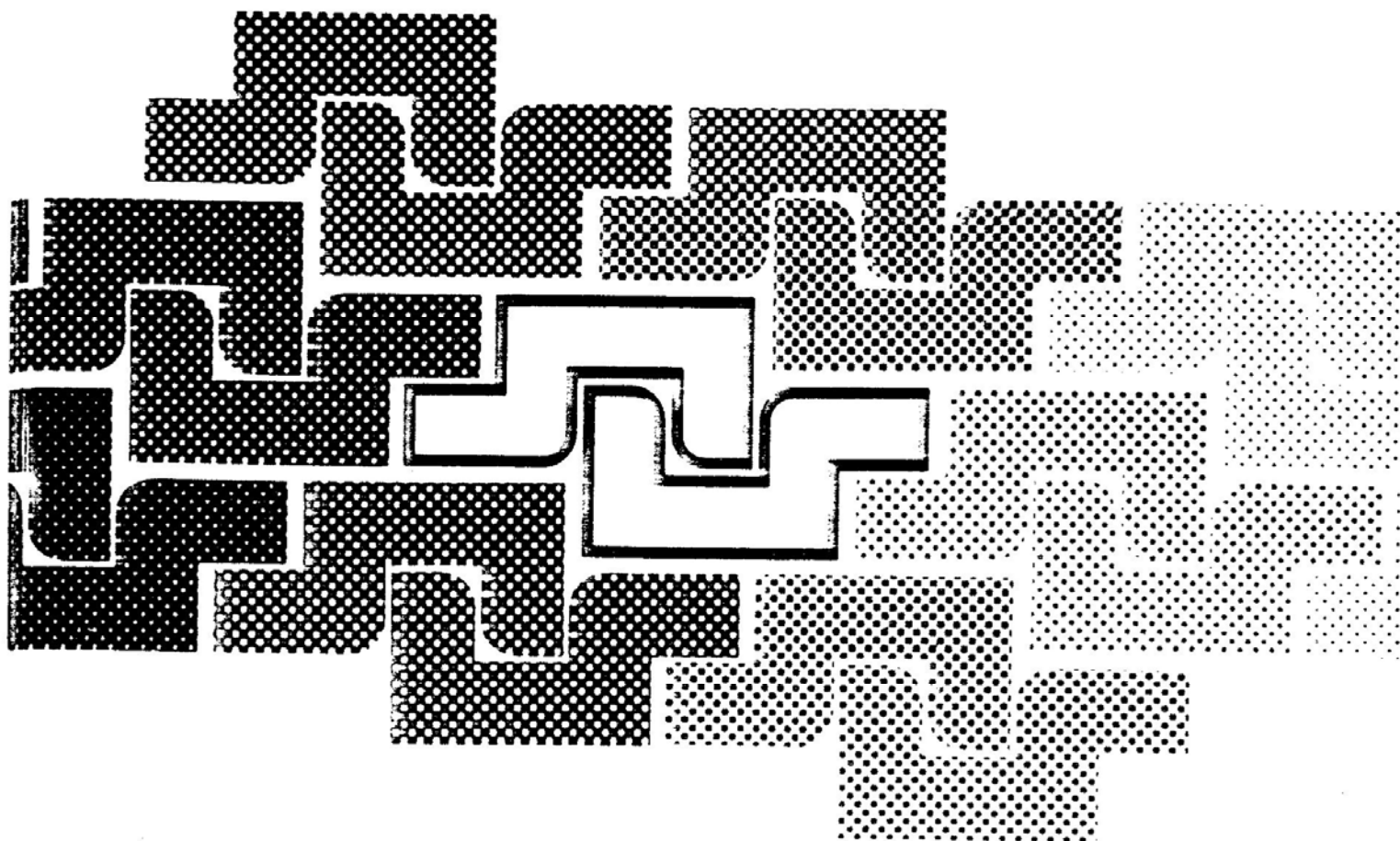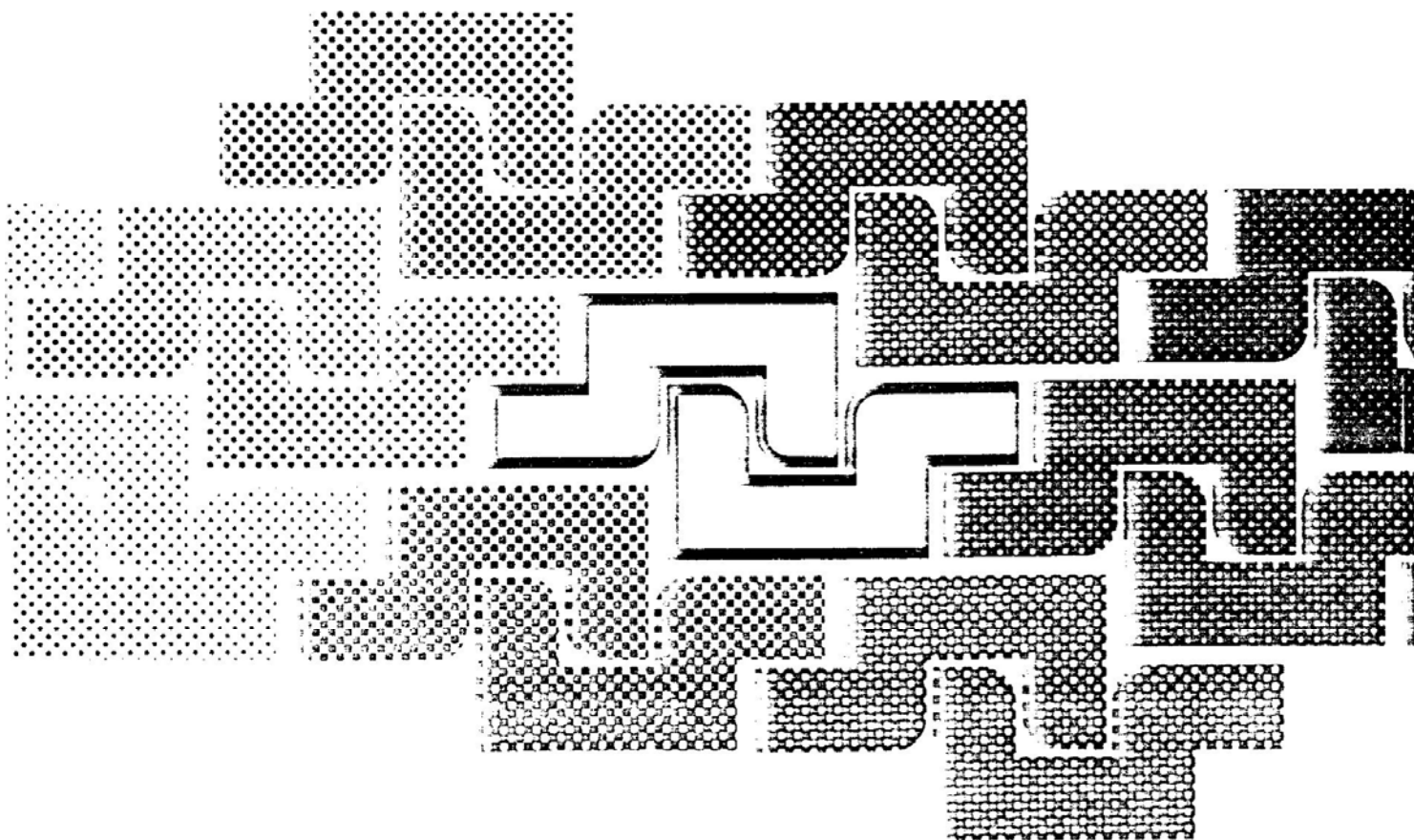
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