CHAPTER

Chaperones as Parts of Cellular Networks

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Abstract

The most important interactions between cellular molecules have a high affinity, are unique and specific, and require a network approach for a detailed description. Molecular chaperones usually have many first and second neighbors in protein-protein interaction networks and they play a prominent role in signaling and transcriptional regulatory networks of the cell. Chaperones may uncouple protein, signaling, membranous, organellar and transcriptional networks during stress, which gives an additional protection for the cell at the network-level. Recent advances uncovered that chaperones act as genetic buffers stabilizing the phenotype of various cells and organisms. This chaperone effect on the emergent properties of cellular networks may be generalized to proteins having a specific, central position and low affinity, weak links in protein networks. Cellular networks are preferentially remodeled in various diseases and aging, which may help us to design novel therapeutic and anti-aging strategies.

Introduction: Cellular Networks and Chaperones

Most of the molecular interactions of our cells have a low affinity, are rather unspecific, and can be described in general terms. An example for this is the self-association of lipids to membranes. However, the most important interactions between cellular molecules have a high affinity, are unique and specific, and require a network approach for a better understanding and prediction of their changes after various environmental changes, like stress.[1-3] One of the good examples for the network description of unique cellular interactions between molecules is the protein-protein interaction network (Fig. 1), where the elements of the network are proteins, and the links between them are permanent or transient bonds.[4-6] At a higher level of complexity we have networks of protein complexes (sometimes built together with lipid membranes), where the individual complexes are modules of the protein-protein network. The cytoskeletal network and the membranous, organellar network are good examples of these, larger networks. In the cytoskeletal network, we have individual cytoskeletal filaments, like actin, tubulin filaments, or their junctions as the elements of the network, and the bonds between them are the links. In the membranous, organellar network various membrane segments (membrane vesicles, domains, rafts, of cellular membranes) and cellular organelles (mitochondria, lysosomes, segments of the endoplasmic reticulum, etc.) are the elements, and they are linked by protein complexes and/or membrane channels. Both the membranes and the organelles contain large protein-protein interaction networks. In signaling networks the elements are proteins or protein complexes and the links are highly specific interactions between them, which undergo a profound change (either activation or inhibition), when a specific signal reaches the cell.[7] In metabolic networks the network elements are metabolites,

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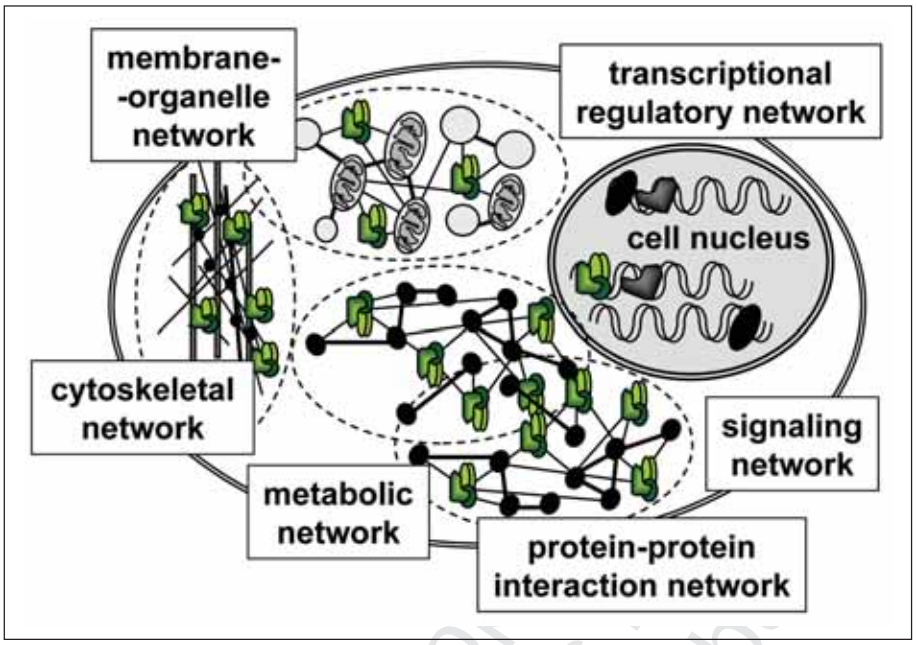

Figure 1. Cellular networks. The figure illustrates the most important networks in our cells. The protein-protein interaction network, the cytoskeletal network and the membranous, organellar networks provide a general scaffold of the cell containing the physical interactions between cellular proteins. Other networks, like the signaling, transcriptional, or metabolic networks are functionally defined. In the signaling network elements of various signaling pathways are linked by the interactions between them. In the transcriptional regulatory network the elements are the transcription factors and the genes, and the connecting links are functional interactions between them. In the metabolic network we have the various metabolites as elements and the enzyme reactions as links. All these networks highly overlap with each other, and some of them contain modules of other networks.

such as glucose, or adenine, and the links between them are the enzyme reactions, which transform one metabolite from the other.[8] Finally, gene transcription networks have two types of elements, transcriptional factor-complexes and the DNA gene sequences, which they regulate. Here the transcriptional factor-complexes may initiate or block the transcription of the gene's messenger RNA. The links between these elements are the functional (and physical) interactions between the proteins (sometimes RNAs) and various parts of the gene sequences in the cellular DNA.[9]

Cellular networks are often small worlds, where from a given element any other elements of the network can be reached via only a few other elements. Networks of our cells usually have a scale-free degree distribution, which means that these networks have hubs, i.e., elements, which have a large number of neighbors. These networks are rich in motifs, which are regularly appearing combinations of a few adjacent network elements, and contain hierarchical modules, or in other words: are forming hierarchical communities.[1-3] The complex architecture of cellular networks is needed to fulfill four simultaneous tasks (Fig. 2). (1) The first task is the local dissipation of the perturbations/noise coming from outside the cell, and from the stochastic elements of intracellular reactions. (2) The second task is the efficient and reliable global transmission of signals from one distant element of the cell to another. (3) The third task is the

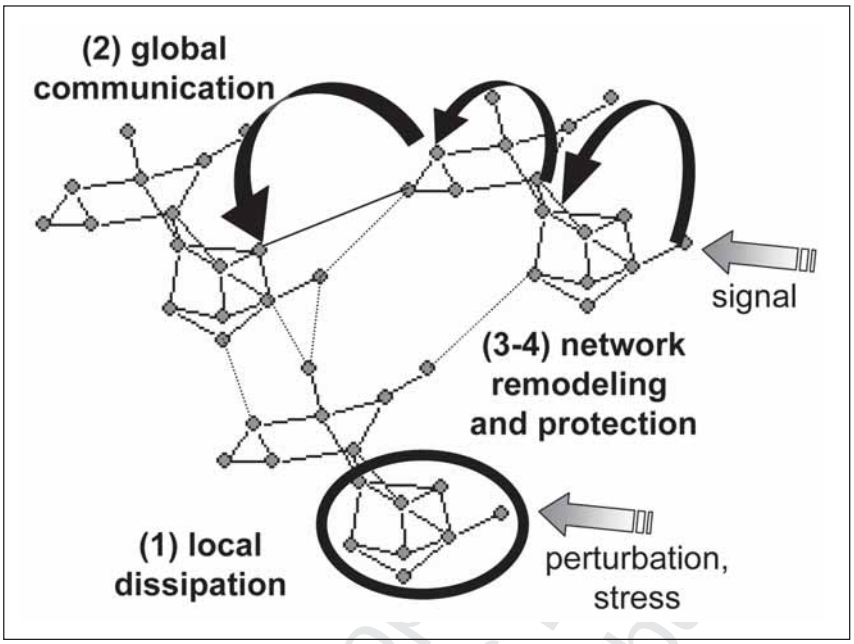

Figure 2. Major tasks of cellular networks. (1) Local dissipation of the perturbations/noise coming from outside the cell, and from the stochastic elements of intracellular reactions. (2) Efficient and reliable global transmission of signals from one element of the cell to another. (3) Discrimination between signals and noise via the continuous remodeling of these networks during the evolutionary learning process of the cell. (4) Protection against the continuous random damage of free radicals and other harmful effects during stress and aging.

discrimination between signals and noise via the continuous remodeling of these networks during the evolutionary learning process of the cell. (4) The fourth task is the protection against the continuous random damage of free radicals and other harmful effects during stress and aging. During the execution of these tasks the assembly of network elements produces a vast number of emergent properties of networks, which can only be understood, if we study the whole network and cannot be predicted knowing the behavior of any of its elements.

The cellular networks use all their features mentioned above to solve their tasks. As a relatively simplified view, hubs help to confine most of the perturbations to a local environment, while the small world character allows the global propagation of signals. Motifs and hierarchical modules help both the discrimination between the two, and provide stability at the network level (which is helped by a number of repair functions at the molecular level).[3] However, this summary of the major features of cellular networks is largely a generalization, and needs to be validated through critical scrutiny of the datasets, sampling procedures and methods of data analysis at each network examined.[10-12]

Molecular chaperones mostly form low affinity, dynamic temporary interactions (weak links) in cellular networks (Table 1).[13,14] Chaperones generally have a large number of partners, thus they behave like hubs of protein-protein interaction or transcriptional regulatory networks.[15,16] Moreover, many chaperone effects (like cell survival, changes in the phenotype diversity, etc.) are typical emergent network properties, which can rarely be understood by studying exclusively the individual chaperone/client interactions. Thus the network approach is a promising tool to explain some key aspects of chaperone function.[17]

Table 1. High and low confidence chaperone neighbors in the yeast protein-protein interaction network

Chaperone Class	High Confidence Partners	Low Confidence Partners
Hsp70	0	28
Hsp90	0	30
Average	1	19

The mean of the partners of the respective chaperone classes (containing the cochaperones as well) was calculated using the annotated yeast protein-protein interaction database of reference 4. High confidence partners are enriched in high affinity chaperone-neighbor interactions. Low confidence partners may contain a considerable amount of artifacts, but may also be enriched in low affinity chaperone-neighbor interactions. The average is the average number of neighbors of all proteins in the database. The differences between the chaperone class values and the average values were not significant due to the high S.D.

Chaperones in Cellular Networks

Chaperones form large complexes and have a large number of cochaperones to regulate their activity, binding properties and function.[18-21] These chaperone complexes regulate local protein networks, such as the mitochondrial protein transport apparatus as well as the assembly and substrate specificity of the major cytoplasmic proteolytic system, the proteasome.[22-24] Chaperones may be important elements to promote the cross-talk between various signaling processes. The Hsp90 chaperone complex promotes the maturation of over a hundred kinase substrates.[14,15] Chaperones have a large number of second neighbors in the yeast protein-protein interaction network (Table 2). The large proportion of hubs in the close vicinity of chaperones gives a central position to these proteins in the protein-protein network, which may help the chaperone-mediated cross talk between signaling pathways.

Chaperones have an important role in membrane stabilization.[25-27] Their membrane association links chaperones to the membrane network of the cell integrating the plasma membrane, the endoplasmic reticulum (ER), the Golgi apparatus, various vesicles, the nuclear membrane and mitochondria together.[28-30]

Table 2. First and second neighbors of molecular chaperones in the yeast protein-protein interaction network

Chaperone Class	First Neighbors	Second Neighbors	% of Hub Neighbors
Hsp70	31	93	41
Hsp90	33	137	49
Average	25	60	28

The mean of the number of first and second neighbors of the respective chaperone classes (containing the cochaperones as well) was calculated using the annotated yeast protein-protein interaction database of reference 4. Hubs are neighbors having more than a 100 interacting proteins. The average is the average number of neighbors of all proteins in the database. The differences between the chaperone class values and the average values were not significant due to the high S.D.

At the end of seventies Porter and coworkers reported various and often quite poorly identifiable, cytoplasmic filamentous structures and called them the microtrabecular network of the cytoplasm.[31,32] Although a rather energetic debate has developed about the validity of the electron microscopic evidence of the microtrabeculae, several independent findings support the existence of the cytoplasmic macromolecular organization.[33-37] This cytoplasmic meshwork not only serves as a scaffold to organize and direct macromolecular traffic, but may also behave as a mesh modulating cytoplasmic streaming assumed to be in the range of 1 to 80 μm/sec.[35] The major cytoplasmic chaperones (TCP1/Hsp60, Hsp70 and Hsp90 and their associated proteins) may well form a part of this cytoplasmic macromolecular network.[38,39]

Molecular chaperones translocate to the cell nucleus, and protect it after stress by a direct protection and repair of damaged proteins, and by changing the intranuclear traffic and nuclear organization.[40,41] Stress-induced nuclear translocation of chaperones may preserve the nuclear remodeling capacity during environmental damage protecting the integrity of DNA. Additionally, chaperones regulate both the activation and the disassembly of numerous transcriptional complexes, thus chaperones emerge as key regulators of the transcriptional network.[42,43]

De-coupling of network elements and modules is a generally used method to stop the propagation of damage.[1-3] When the cell experiences stress, chaperones become increasingly occupied by damaged proteins. This, together with the stress-induced translocation of chaperones to the nucleus mentioned before, might lead to an "automatic" de-coupling of all chaperone-mediated networks including protein-protein, signaling, transcriptional regulatory as well as membranous, organellar networks providing an additional safety measure for the cell.[17]

Chaperone-Mediated Emergent Properties of Cellular Networks

As we have seen before, chaperones are involved in the regulation of signaling, membranous, organellar, cytoskeletal and transcriptional networks. However, relatively little is known on the chaperone-mediated, emergent properties of cellular functions. As mentioned before, these emergent properties are properties of the cell, or the whole organism, which can not be linked to the behavior of any of their particular elements, but emerge as a concerted action of the whole cellular network. One of the best examples of chaperone-mediated emergent network properties was shown by Susannah Rutherford and Susan Lindquist, when they discovered that Hsp90 acts as a buffer to conceal the phenotype of the genetic changes in *Drosophila melanogaster*.[44] Chaperone-induced genetic buffering is released upon stress, which causes the sudden appearance of the phenotype of previously hidden mutations, helps population survival and gives a possible molecular mechanism for fast evolutionary changes. On the other hand, the stress-induced appearance of genetic variation at the level of the phenotype cleanses the genome of the population by allowing the exposure and gradual disappearance of disadvantageous mutations by natural selection. After the initial report of Rutherford and Lindquist in reference 44 on Hsp90, the effect was extended to other chaperones and to *Escherichia coli*, *Arabidopsis thaliana* and the evolution of resistance in fungi.[45-47] The Hsp90-mediated buffering might have an epigenetic origin due to the Hsp90-induced heritable changes in the chromatin structure.[48]

Chaperones are highly conserved proteins, therefore similar mechanisms might operate in humans.[49] Moreover, the tremendous advance of medicine and the profound changes in human lifestyle in the last two hundred years significantly decreased natural selection, and potentially helped the accumulation of hidden mutations in the human genome. In the first approximation this is not a problem, since we have a large amount of chaperones and other buffering systems to hide these disadvantageous mutations. However, the amount of damaged or newly folded proteins and the available chaperone capacity are two sides of a carefully balanced system in our cells. An excess of chaperone substrates or diminished chaperone content might both induce a "chaperone-overload", i.e., a relative deficit of available active, unloaded chaperones.[50] Chaperone overload becomes especially large in aged subjects, where protein damage is abundant, and both chaperone induction and chaperone function are impaired. A special case

of chaperone-overload occurs in folding diseases including various forms of neurodegeneration, such as Alzheimer's disease, Parkinson's disease or Hungtington's disease, where a misfolded and usually not degraded protein sequesters most chaperones.[50-53] In consequence of the chaperone overload, the protein products harboring the "hidden mutations" may be released, and may contribute to the development of civilization diseases, such as cancer, atherosclerosis and diabetes. Since relatively few generations have been passed from the beginning of the medical revolution and lifestyle changes in the 19th century, this effect is most probably negligible today. However, it increases with each generation. Still, we probably have many hundreds of years to think about a possible solution, which gives us time to learn much more and reconcile the serious ethical concerns with a possible solution.[50]

In recent years the scientific community has became increasingly aware of the idea that not only chaperones but a large number of other proteins may also regulate the diversity of the phenotype.[3,14,54-56] Though a relatively small number of regulators were uncovered yet, a common molecular mechanism, such as the involvement in signaling or modifications of histones and DNA structure seems to be an unlikely explanation for all the effects observed. If a general explanation is sought, it is more likely to be related to the network properties of the cell. In this context, chaperones are typical weak linkers, providing low affinity, low probability contacts with other proteins (for a grossly simplified illustration, see Table 1). Weak links are known to help system stability in a large variety of networks from macromolecules to social networks and ecosystems, which may be a general network-level phenomenon explaining many of the genetic buffering effects. Currently we do not know, what position is required, if any, in the network for these 'weak links' besides their low affinity and transient interactions. The central position of chaperones demonstrated in Table 2 may be an additional hallmark of stabilizing weak links.[3,14]

Chaperone Therapies

Cellular networks are remodeled in various diseases and after stress. Proper interventions to push the equilibrium towards the original state may not be limited to single-target drugs, which have a well-designed, high affinity interaction with one of the cellular proteins. In agreement with this general assumption, several examples show that multi-target therapy may be superior to the usual single-target approach. The best known examples of multi-target drugs include Aspirin, Metformin or Gleevec as well as combinatorial therapy and natural remedies, such as herbal teas.[57] Due to the multiple regulatory roles of chaperones, chaperone-modulators provide additional examples for multi-target drugs. Indeed, chaperone substitution (in the form of chemical chaperones), the help of chaperone induction and chaperone inhibition are all promising therapeutic strategies.[58-61]

Conclusion

Chaperones regulate cellular functions at two levels. In several cases they interact with a specific target protein, and become mandatory to its folding as well as for the assistance in the formation of specific protein complexes (and in the prevention of the assembly of others). These specific interactions make chaperones important parts of the core of cellular networks, such as the protein net, the signaling network, the membranous and organellar network as well as the transcriptional network. However, in most cases chaperones have only a low affinity, temporary interactions, i.e., 'weak links' with most of their targets. Changes of these interactions do not affect the general behavior of the whole network, the cell. However, an inhibition of these weak links might lead to a rise in cellular noise, the destabilization and des-integration of the whole network. By this complex version of the 'error-catastrophe', chaperone inhibitors help us to combat cancer. In contrast, chaperone activation may decrease cellular noise, stabilize and integrate cells and thus give a general aid against aging and diseases. Thus, besides slowing the development or reversing protein folding diseases, chaperone-therapies may also generally benefit the aging organism by stabilizing its cells and functions. Properly working

chaperones may be key players to help us to reach improved life conditions in an advanced age. The assessment of the multiple roles of chaperones in the context of cellular networks is only just beginning.

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