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THE CHAPERONING SYSTEM: PHYSIOLOGY AND PATHOLOGY

[Il sistema delle chaperonine: fisiologia e patologia]

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Abstract. The concept of chaperoning system is presented here for the first time. The system encompasses all the molecular chaperones and their anatomically and functionally related molecules and higher order structures (multimolecular assemblies, cells, tissues). This ensemble of functionally related molecules and structures is viewed as a physiological system whose central role is the control of protein homeostasis in what concerns maintenance of a complete set of proteins in all fluids, cells, and tissues with the correct, native, functional conformation. The system ensures proper protein folding, re-folding, degradation, and translocation, and participates in a wide range of other molecular and cellular processes from antigen presentation to hormone receptor assembly and ligand binding, and others, that require stabilization of structure and facilitation of intermolecular interaction. The science that studies this system is called chaperonology, which also includes the study of disease caused by system malfunction and defective chaperones, i.e., the chaperonopathies, and their prevention and treatment using chaperone genes or proteins, i.e., chaperonotherapy.

Riassunto. Viene presentato, per la prima volta, il concetto dell'esistenza di un sistema degli chaperoni molecolari. Questo sistema comprende tutti gli chaperoni molecolari e le molecole strutturalmente e funzionalmente correlate, tanto quanto strutture di livello superiore (complessi multimolecolari in cellule e tessuti). Questo insieme di molecole e strutture funzionalmente correlate tra di loro viene descritto come un "sistema fisiologico" il cui ruolo centrale è il controllo dell'omeostasi proteica, specie per ciò che concerne il mantenimento della corretta (nativa) conformazione funzionale di proteine presenti in tutti i fluidi biologici, così come nelle cellule e nei tessuti. Questo sistema, quindi, assicura il corretto folding delle proteine, così come il loro re-folding, ma anche la degradazione e la traslocazione; inoltre partecipa ad un elevato numero di altre attività cellulari e molecolari, che vanno dalla presentazione antigenica all'assemblamento dei recettori ormonali, dalla formazione di complessi con ligandi ad altre azioni che richiedono la stabilizzazione delle strutture proteiche e la facilitazione dell'interazione tra molecole. La scienza che studia questo sistema è detta chaperonologia, e questa include anche lo studio delle malattie determinate dal suo malfunzionamento (c.d. chaperonopatie), come ad esempio per la presenza di chaperoni "difettosi", nonché il loro utilizzo in ambito preventivo e terapeutico (c.d. chaperonoterapia), attraverso l'espressione genica o l'utilizzo delle stesse proteine.

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Introduction

Since 1962 the response to stress has been studied at various levels [1]. The stressor often tested was, and is still today, a temperature elevation, heat shock. However, there are many other stressors of various natures, chemical, physical, mechanical, biological, psychological, social, occupational, etc., which have also been investigated [2,3]. One consequence of stress that was examined from the beginning was the response of certain genes to heat shock which resulted in the production proteins called heat-shock proteins (Hsp). The functions of Hsp were then studied in various ways and some were found to assist protein folding and were called molecular chaperones [1]. Work on Hsp and chaperones has been performed over many years in many laboratories around the world and the results have been published in a broad range of printed and electronic publications, and made available also in databases. Thus, a huge amount of data and ideas about stress, stress response, Hsp, chaperones, and anti-stress mechanisms is disperse in a wide variety of sources. A few years ago we started the unification of the field into a coherent rational structure, a new scientific discipline we called chaperonology [4,5]. This new discipline includes subspecialties such as chaperonomics, chaperonotherapy, and the study of chaperonopathies [4-6].

In this article, we propose the unification of the molecular chaperones and Hsp molecules and the higher order structures anatomically and functionally related to these molecules into a single physiological system.

Physiology. Definitions

Chaperoning system

The chaperoning system is a newly identified physiological set of molecules and molecular teams, and pertinent cells and tissues, key to maintaining protein homeostasis and other cellular functions. The molecular components of the system have been known for sometime but they were not considered as members of a single physiological system until now. Likewise, the cells containing chaperones and/or producing the chaperones were not considered before as part of a specialized physiological system centered on chaperones.

Terminology

The ensemble of chaperones and closely related molecules in terms of interaction and function and pertinent supramolecular structures (multimolecular machines, cells, tissues) could be considered a system or an apparatus. System was chosen over apparatus because of its connotation of interconnected functions and pathways made of chaperones and related molecules and cells and tissues, whereas apparatus has a less open-ended feel as

it keeps the focus on the "hardware" molecules.

The system could be named in various ways, for instance the chaperone system, the chaperonic system, or the chaperoning system. We have chosen at this time the term chaperoning system because chaperone system may be taken to: a) designate the system pertaining to a single chaperone from among the many that exist; b) indicate that the chaperones' only function is to assist (to chaperone) nascent not yet folded polypeptides and unfolded proteins to gain or regain a folded, native conformation when, in fact, chaperones have other functions, too; and c) exclude components of the system that are not typical chaperones but interact with them in a critical way, or that are not molecules, such as the cells that contain and/or produce the chaperones.

The term chaperonic system was not preferred either because the spoken change of emphasis, from the soft "…one" of chaperone to the hard "…onic" of chaperonic is both unattractive to the ear and non-intuitive. Furthermore, chaperonic does not reflect as well as chaperoning does the functions and interaction of the components of the system.

Chaperonology

The identification of the central components of the chaperoning system, the molecular chaperones, has originated the novel field of science named chaperonology. Chaperonology deals with the chaperoning system and with its components, molecules and higher order structures (molecular assemblies, cells, tissues), and their abnormalities and pathologies.

The roles of chaperones

The classic concept is that chaperones assist other proteins to fold and re-fold, and usher defective proteins toward degradation. Thus, chaperoning proteins to fold or refold and guiding proteins toward degradation can be considered typical functions of chaperones. However, many chaperones play roles that are not typically related to protein folding but are seemingly quite different, for example the role of Hsp70 in tumor-antigen presentation and tumor immunity [7,8]. These could be considered atypical functions of typical chaperones. Conversely, molecules that are not typical chaperones may have functions similar to the atypical functions of typical chaperones. For example, Hsp32 is the product of a heat shock-inducible gene that plays a significant role in protection against oxidative stress but has no known function in protein folding or refolding [9]. Thus, Hsp32 is a typical heat-shock protein with a role in anti-stress mechanisms like many chaperones but it is not a typical chaperone.

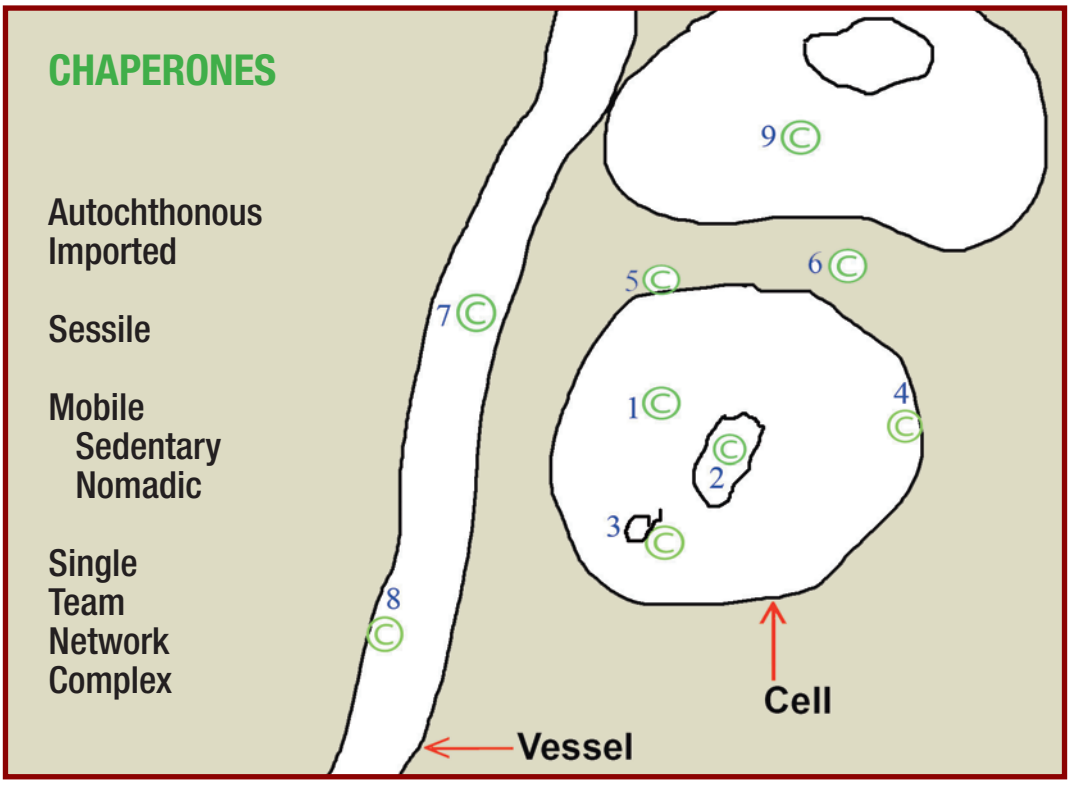

Fig. 1

Subpopulations of chaperones: autochthonous vs. imported (with regard to any given cell); sessile vs. mobile (the latter can be sedentary or nomadic); single or member of a chaperoning team with other chaperones, co-chaperones, and co-factors, also named chaperoning machine. A chaperoning team or machine can be a member of a chaperoning network, which is formed by various chaperoning teams and, possibly, other molecules or molecular assemblies.

A chaperone can also form a complex with another molecule or structure (tumor antigen, cell-surface receptor, cytosolic glucocorticoid-hormone receptor, chemical compound), but in this case the complex is not a chaperoning machine; it has other functions more or less unrelated to chaperoning. Examples: 1) Hsp70 forms complexes with tumor antigens (peptides) and cell-surface receptors; 2) Hsp90 binds glucocorticoid-hormone receptor (a protein which is a transcription factor); 3) Hsp90 binds some anti-tumor compounds like the antibiotic geldanamycin. See text for references.

Key. Circled C, molecular chaperone; 1, mobile chaperone in the cytosol; 2, chaperone inside an organelle, such as the nucleus or mitochondrion; 3, sessile chaperone anchored to a particle (e.g., ribosome) in the cytosol; 4 and 5, sessile chaperone anchored to the cell membrane on the cytosolic side (4) or on the outside in the extracellular space (5); 6, mobile chaperones in the intercellular space; 7, mobile chaperone in circulation inside a vessel (blood or lymph); 8, sessile chaperone anchored to the vessel wall on the inside; 9, mobile chaperone in the cytosol like that shown in 1, but imported from another cell. Molecular chaperones can be found also in other locations such as cerebrospinal fluid and secretions (e.g., saliva and urine), not shown in this figure (see Table 3)

Molecules, cells and tissues of the chaperoning system

Chaperones are made in cells for work in the same cells in which they are made or for export (Fig. 1). Chaperones for export are made in a cell and then travel to other locations, inside cells or in extracellular sites, in which they will take residence and work. It can be predicted that there are cells, and tissues or defined zones within certain tissues or organs, specialized in the production of chaperones for export.

Chaperones are present in tissues and fluids and, as explained earlier, we call the entire chaperone population of an organism the chaperoning system (Fig. 1). Each cell has its own set of chaperones or subsystem that typically includes more than one chaperoning complex or team, and teams interact forming networks inside the cell.

Pertinent timely questions

The words molecular chaperones and chaperoning system immediately suggest a number of issues and questions (Table 1). Answers to some of these questions can be found in this article and in the bibliography.

Table 1: Questions
What are the components of the chaperoning system?
Where and when are the molecular chaperones made?
Where do the chaperones reside and work?
What do the chaperones do?
What are the diseases caused by defective chaperones?
What types of chaperonopathies are known?
How would one diagnose a chaperonopathy?
When would treatment with chaperones, i.e., chaperonotherapy, be indicated?
What types of chaperonotherapies are available?
What to do next?

Classification of molecular chaperones

A) Types of chaperones according to their size (molecular weight)

Heat-shock proteins (Hsp) senso stricto are the product of genes induced by a temperature elevation (heat shock), but the name is also applied to proteins from genes inducible by any other stressor. Many Hsp are chaperones (for example the heat-inducible form of Hsp70 in humans) but not all chaperones are Hsp. An example of the latter is the Alpha-Hemoglobin Stabilizing Protein (AHSP), which is a dedicated chaperone whose substrate is the alpha hemoglobin chain and is encoded in a gene not known to be inducible by heat or any other stressor [10]. Conversely, many Hsp are not chaperones, for example Hsp32 or

heme oxygenase-1 (HO-1). This enzyme is the inducible isoform of heme oxygenase that catalyzes the NADPH, O_2 and cytochrome P450-reductase dependent oxidation of heme to carbon monoxide, iron, and biliverdin, which is immediately reduced to bilirubin [9]. Thus Hsp32 is associated with the generation of biliverdin and bilirubin, potent antioxidants, and therefore it has to be considered part of the anti-stress mechanisms of which many molecular chaperones are important components.

Although many Hsp do not act as chaperones and, vice versa, many chaperones are the product of genes not inducible by any stressor, the terms Hsp and chaperone have been used as synonyms for years in a huge number of printed and electronic publications, and in databases. It is virtually impossible at this time in the history of chaperonology to correct these abuses in nomenclature usage. Therefore, we use here both terms as synonyms.

Hsp-chaperones can be grouped according to their size in a classification that has practical utility in research and, particularly in pathology and clinics (Table 2).

Table 2: Classification of Hsp-chaperones according to molecular weight[1]

Chaperone subpopulation		
Name	Other names	MW (kDa)
Heavy	High MW; Hsp100	100 or higher
Hsp90		81-99
Hsp70	Chaperones; DnaK	65-80
Hsp60	Chaperonins; Cpn60	55-64
Hsp40	DnaJ	35-54
Small Hsp	sHsp; alpha-crystallins	34 or less
Other	Proteases; isomerases; AAA+ proteins (e.g., paraplegin, spastin]), etc.	Various

[1]From references [2,20]

B) Types of chaperones according to their origin with regard to their place of residence and work

Chaperones are in fixed locations inside the various cell compartments as well as in biological fluids moving around (Fig. 1; Table 3).

Note: The following two terms refer to chaperones inside any given cell without taking into account the cell's organelles or membranes.

Autochthonous: a chaperone originated in the cell in which it resides. The cell of origin and of residence is one and the same, i.e., an autochthonous chaperone resides and works in the same cell in which it was produced, disregarding in which cell compartment the chaperone resides and works. *Imported:* the place of residence (a given cell) of an imported

chaperone is not the same as that of its origin but another cell.

Table 3: Places at which chaperones reside and work	
Location	Compartment
Cellular	Nucleus
	Cytosol
	Mitochondria
	Endoplasmic reticulum
	Lysosomes
	Vesicles
	Membrane on the inside
	Chloroplasts
Pericellular	Membrane on the outside
Extracellular	Intercellular space
	Blood (plasma, serum)
	Cerebrospinal fluid
	Secretions (e.g., saliva)

C) Types of chaperones according to their ability to move and change residence

Chaperones can be classified according to their mobility (Fig. 1). *Sessile:* fixed, anchored to another structure (e.g., cell membrane). *Mobile:* not fixed, capable of moving inside a cell (e.g., from cytosol to nucleus), or outside cells (e.g., in the blood) and change place of residence and work. Mobile chaperones can be of two subtypes: *i) Sedentary*, reside always in the same cell or cell compartment but are not fixed to any structure, so they can move within the confines of their "home" or cellular realm; and *ii) Nomadic*, change residence, i.e., the chaperone takes residence for a while in one location (e.g., a cell or cell compartment), then in another, and so forth. Nomadic chaperones travel and work in various successive places. Hsp60 is an example of mobile, nomadic chaperone: it is produced in the cytosol and then translocated to the mitochondria from which it can exit and go back to the cytosol, and even exit the cell and appear in the extracellular space [11,12].

D) Types of chaperones according to their relation with other chaperones or other molecules

Chaperones exercise their functions alone or in associations with other molecules (Fig. 1), and they can be considered *Single*, i.e., a chaperone molecule that performs its role not associated with any other chaperone, or *Social*. The latter form part of a *Team (more precisely, Chaperoning Team)*, namely, a specific association of chaperones to build a chaperone machine. A Chaperoning Team includes chaperones senso stricto (e.g., Hsp70[DnaK]), co-chaperones (e.g., Hsp40[DnaJ]), and co-factors (e.g., Nucleotide Exchange Factor [NEF]

such as GrpE); all these molecules assemble into a multimolecular machine that performs the chaperoning work. Other associations are: *Network (more precisely, Chaperoning Network)*, which is a specific interaction between chaperone machines (e.g., Hsp70-Hsp40-NEF, and Hsp60-Hsp10, and Prefoldin), or between a chaperoning team and a single chaperone. *Complex* designates the association of a chaperone with another molecule which is not a chaperone, for example Hsp70 with tumor antigen [7,8], Hsp90 with glucocorticoid receptor [13] or with geldanamycin and other inhibitors [14-16], and Hsp60 with procaspase-3 [17].

E) Other classifications of chaperones

Chaperones can be classified according to gene type into house-keeping vs. anti-stress (constitutive vs. stress-inducible genes, respectively); and according to substrate range into generic vs. dedicated (with many, almost any, client polypeptide vs. with a single, specific client polypeptide or with a very restricted, specific set of client polypeptides, respectively).

Table 4: Chaperonopathies[1]

Type		
Genetic	Examples	References
Mutation hereditary	AlphaA-crystallin gene, cataracts. AlphaB-crystallin gene, desmin-related myopathy. Hsp27 (HSPB1) dHMN/CMT2[2]	[22-24]
Mutation sporadic	Hsp27 (HSPB1) dHMN/CMT2	[24]
Polymorphism		
Protein coding region	HSP70-1 (HspA1A); HSP70-2 (HspA1B); HSP70-Hom (HspA1L) Affect longevity	[25]
Non-coding region: promoter region (5' UTR)	HSP70-1 (HspA1A); HSP70-2 (Hsp70A1B) Affect longevity	[25]
Acquired		
Early onset	Alpha-crystallin PTM (cataracts in diabetes)	[26]
Late onset	Alpha-crystallin PTM (cataracts of senescence)	[27,28]
By mistake		
Tumors	Increased: Hsp60 & Hsp10, colon, exocervix, prostate; Hsp90, breast; HYOU-1, breast, brain	[29-35]
	Decreased: Hsp10 and Hsp60, lung	[33,36]
	Hsp70 necessary: breast	[37]
Other	Prefoldin generates highly toxic Abeta oligomers rather than the less toxic fibrils (ref. Alzheimer's disease)	[38]

[1]Other examples of chaperonopathies can be found in references [4,5,20,21].
[2]Abbreviations: dHMN/CMT2, distal Hereditary Motor Neuropathy/Charcot-Marie-Tooth disease type 2; UTR, untranslated region; PTM, post-translational modification; Hsp, heat-shock protein.

Pathology. Disorders of protein homeostasis

Identification of chaperones and their functions made clear that the chaperoning system is a major component of anti-stress mechanisms and also plays a central role in protein homeostasis, particularly in what concerns the maintenance of a complete set of proteins with a native, functional conformation throughout the cell and the organism. The realization that chaperones normally play such important roles lead to the idea that malfunctional, defective chaperones must have a role in pathogenesis [2,18,19]. Pathological disorders in which abnormal (sick) chaperones play a pathogenetic role were called chaperonopathies [18-21].

Protein precipitates. Here we consider protein precipitates a key indicator of protein homeostasis abnormality or failure. As when hyperglycemia is detected one thinks of problems with insulin and the pancreas, protein precipitates ought to direct attention to chaperones, i.e., to a defect in the chaperoning system or chaperonopathy.

Chaperonopathies. The abnormalities and pathologies of the chaperones are grouped under the newly coined name of chaperonopathies. The most common chaperonopathies are manifestations of ageing [18]. A classification of chaperonopathies is displayed in Table 4.

Chaperonopathies by mistake or collaborationism. Pathologic conditions in which normal chaperones are involved in pathogenetic pathways and contribute to the development of disease rather than the contrary are called chaperonopathies by mistake or collaborationism. Significant examples of chaperonopathies by mistake are some types of cancers (Table 4).

Treatment

Chaperonotherapy. Identification of chaperonopathies and other diseases (e.g., protein-misfolding diseases) in which normal chaperones could play a beneficial role has lead to the idea of using these molecules for treatment, namely chaperonotherapy [4,5].

Chaperonotherapy refers to the use of chaperones (genes and proteins) for treatment of chaperonopathies, for example replacement of a structurally defective chaperone with a normal version of it, or supplementation of a quantitative deficiency of a chaperone by administering the pertinent chaperone as gene or protein. Chaperonotherapy can also be used for treatment of conditions that are not chaperonopathies at all, or are not primarily chaperonopathies (e.g., some neurodegenerative diseases) but are due primarily to abnormalities in proteins (proteinopathies) that are not chaperones.

Treatment of chaperonopathies by mistake, such as certain forms of cancer, requires anti-chaperone agents. When chaperones are involved in pathogenetic pathways and contribute to the development of disease rather than the contrary they must be inhibited or eliminated.

Development of antichaperone agents is one of the most promising lines of research in the fight against cancer.

Conclusions

A new physiological system is presented that plays a central role in controlling protein homeostasis at the level of molecular conformation. Proteins are major cellular and organismal components with a broad range of functions. For a cell or organism to function correctly all its proteins in all its compartments must be at the physiological concentrations and possess the right primary, secondary, tertiary and, when pertinent, quaternary structures. The chief function of the chaperoning system is to ensure that all proteins reach after synthesis the mature, correct functional structure beyond the primary one, i.e., the native conformation. The chaperoning system also monitors the native conformation of mature proteins and restores it if these proteins tend to lose it due to stress or any other protein-denaturing factor. Furthermore, the components of the system play a variety of other roles, many of which are not those typically assigned to chaperones (e.g., assisting nascent proteins to fold correctly or to refold if partially denatured, helping protein translocation across membranes, or ushering damaged or unnecessary proteins toward degradation) but are diverse, including in many instances facilitation of intermolecular association and interaction and stabilization of multimolecular assemblies. The system encompasses molecules, cells and tissues but the central components are the molecular chaperones. System malfunction causes disturbances in protein homeostasis that lead to aggregation and formation of protein precipitates. Failure of chaperones due to qualitative or quantitative abnormalities cause pathological conditions named chaperonopathies. Treatment of these conditions can be done using chaperone genes or proteins, a form of therapy called chaperonotherapy.

Perspectives

The concept of chaperoning system offers a new standpoint to look at molecular chaperones and their associated molecules and higher order structures and to study these molecules and structures using fresh approaches, including those that will take into consideration interactions and interconnections between system components far apart in the cell and in the organism. Likewise, the new concept will be instrumental to unveil aspects not yet completely understood of known diseases. This unveiling of new features will, in turn, provide clues on the strategies and methods that should be used for elucidating them. Also, the chaperoning system concept, in showing new angles of pathologic disorders still poorly characterized, will allow the investigation of these disorders using novel strategies that should uncover details as yet hidden.

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