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CHAPEROME: HISTORICAL PERSPECTIVE AND CURRENT CONCEPTS

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Abstract. The life cycle of cells is accompanied by constant synthesis, transport and degradation of polypeptide chains — proteins and signal sequences. Each polypeptide chain has four levels of structure, and its adoption of the correct spatial conformation is necessary for the expression of the function of the molecule. Hydrophobic interactions or the formation of sulfide bridges can prevent the formation of the correct conformation. Moreover, the high-order structures of proteins are disrupted by various stress responses to the cell. In the course of studying the processes of protein synthesis and aggregation, specific highly conserved proteins were identified that can bind to a newly synthesized or damaged polypeptide, imparting a functional structure due to the sequential connection with recognition domains. These proteins are called molecular chaperones. This includes the superfamily of heat shock proteins, the synthesis of which is a nonspecific cell response to stress. To study the processes of proteostasis, it is necessary to understand that these proteins act only in close relationship with cochaperones and other auxiliary molecules. Such aggregates are called chaperomes, or chaperone machineries, and are of considerable interest in biomedical research. This review discusses the historic perspective for chaperones and chaperome as a supramolecular complex as well as their place in cell proliferation.

Key words: molecular chaperones; heat shock proteins; chaperome.

ШАПЕРОМ: ИСТОРИЧЕСКАЯ ПЕРСПЕКТИВА И СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ

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Резюме. Жизненный цикл клеток сопровождается постоянным синтезом, транспортом и деградацией полипептидных цепей — белков и сигнальных последовательностей. Каждая полипептидная цепь обладает четырьмя уровнями структуры, и принятие ею правильной пространственной конформации необходимо для экспрессии функции молекулы. Препятствовать формированию правильной конформации могут гидрофобные взаимодействия или образование сульфидных мостиков. Более того, структуры высокого порядка белков нарушаются при различных стрессовых ответах на клетку. В ходе исследования процессов синтеза и агрегации белков были выявлены особые консервативные протеины, способные связываться с новосинтезированным или поврежденным полипептидом, придавая за счет последовательной связи с доменами узнавания функциональную структуру. Именно эти белки назвали молекулярными шаперонами. В их число входит суперсемейство белков теплового шока, синтез которых является неспецифичным ответом клетки на стресс. Для изучения процессов протеостаза необходимо понимание, что данные белки действуют лишь в тесной взаимосвязи с кошаперонами и другими вспомогательными молекулами. Такие совокупности называются шаперомом, или шаперонной машиной, и они представляют значительный интерес в биомедицинских исследованиях. В данном обзоре литературы представлены основные исторические этапы понимания шаперонов и шаперома как супрамолекулярного комплекса и их место в жизнедеятельности клетки.

Ключевые слова: молекулярные шапероны; белки теплового шока; шапером.

Thanks to the research of the early twentieth century, it became clear that many polypeptides (typically small single-domain proteins) can easily restore their native structure by themselves in vitro, while others (more complex, multi-domain or oligomeric proteins) adopt the necessary topology only in the presence of additional molecules that are not part of the polypeptide of the final native protein. [22]. These molecules were identified as proteins and were named molecular chaperones. The term “molecular chaperone” was first used in 1968 in order to describe the role of nucleoplasmin in the assembly of DNA and histones into nucleosomes [11]. The name arose from the fact that nucleoplasmin promotes histone-histone interactions with the formation of a correct oligomeric form, preventing aggregation. It does this without forming a part of the nucleosome by itself or defining the modification of the nucleosome. Therefore, nucleoplasmin assumes the role of a chaperone.

Later, the term “molecular chaperone” was expanded to include a widespread chloroplast protein called the RuBiSCo (ribulose bisphosphate carboxylase) large subunit binding protein now known as chloroplast chaperonin, which prevents the formation of insoluble precipitate by newly synthesized large rubisco subunits. These large subunits are known to be prone to improper assembly not because of electrostatic interactions, but because they expose highly hydrophobic surfaces to the aquatic environment. Although early experiments did not determine whether chaperonin promotes folding or assembly, more recent work with mitochondrial chaperonin has proven that this protein functions at the stage of folding [15, 29]. For some time, the term “molecular chaperone” was limited to two proteins; its modern use began with the assumption that its meaning should be expanded to describe the function of a larger group of proteins that were supposed to promote folding and assembly reactions in various cellular processes [9, 17]. Since the 1990s, this definition has been constantly being refined to take into account other discoveries concerning the role of chaperones in the processes of cell proteostasis.

The role of molecular chaperones in the folding, assembly, and intracellular translocation of proteins is a constant subject of research. The following conclusions are valid for normally functioning cells.

Chaperones of organelles such as EPR (endoplasmic reticulum) play a key role in the folding of newly synthesized proteins [16, 23]. Mitochondrial membranes have an isolated population of chaperones responsible for correcting or disassembling proteins damaged during cellular respiration [40].

Cytosolic chaperones play a key role in the folding, transport, and biological activity of a number of proteins used for transport to specific organelles, such as the nucleus and mitochondria [7, 28, 42].

Nuclear chaperones, unlike others, bind to proteins after folding due to ionic forces, and play a supportive role in the structural organization of macromolecular chromatin complexes [30].

Membrane-bound chaperones, found only on cells of solid and hematological tumors, are involved in the proliferation, migration, and immunogenicity of cancer cells [4, 38].

The list of detected chaperones is constantly updated. Enzyme-like cofactors protein disulfide isomerase and peptidyl-prolyl cis-trans-isomerase, which catalyze trans- to cis-proline isomerization and are usually considered as EPR chaperones, were only discovered in 1992 [37]. The chaperone family included both prokaryotic and eukaryotic proteins of different structures and localization.

However, differences in names and the lack of a clear division into families significantly complicated the studies of chaperones. A significant part of human chaperones began to be identified as human heat shock proteins (HSP), stress-sensitive proteins necessary to combat heat and other protein-toxic stresses. Soon after that, in 2003–2005, it became clear that constitutively expressed members such as Hsc70 (HSPA8) in the HSP70 family can also be encoded within the HSP family. This is how the division into stress-induced and constitutive chaperones appeared [18].

With the development of protein crystallography and genetic analysis, the first attempts to improve the classification were made — there appeared a division into families (by molecular weight), within which specific representatives were identified (by coding genes). However, even after analysis of the human genome, the names used for human chaperones in the literature were rather chaotic: up to ten different names could be found for the same gene product. Moreover, almost identical names were used to refer to different gene products. For example, HSPA1B was named HSP70–2, whereas HSP70.2 refers to the member HSPA2, which is specific for testicles. The first steps in dividing chaperones by genes and functions at the same time were only made by 2000.

The revolutionary work of Professor Harold Kampinga was particularly successful in shaping the classification [20]. The proposed nomenclature was based on the encoding assigned by the HUGO Gene Nomenclature Committee and used in the National Center of Biotechnology Information Entrez Gene database for the heat shock genes. In addition to this nomenclature, a list of the human Entrez gene identifiers and the corresponding Entrez gene identifiers for the mouse orthologs was provided. In this work, tables were presented for each superfamily of human chaperones (Fig. 1).

Chaperones seem to act sequentially in protein folding pathways, binding to intermediates that are at various stages of topology formation, and then transferring them to the next chaperone or chaperone complex in the cascade, eventually releasing the competence native protein. Binding usually involves the interaction of chaperones with hydrophobic residues on the surface of unfolded proteins, and

	Gene name	Protein name	Old names	Human gene ID	Mouse ortholog ID
HSP A					
1	*HSPA1A*	HSPA1A	HSP70-1; HSP72; HSPA1	3303	193740
2	*HSPA1B*	HSPA1B	HSP70-2	3304	15511
3	*HSPA1L*	HSPA1L	hum70t; hum70t; Hsp-hom	3305	15482
4	*HSPA2*	HSPA2	Heat-shock 70kD protein-2	3306	15512
5	*HSPA5*	HSPA5	BIP; GRP78; MIF2	3309	14828
6	*HSPA6*	HSPA6	Heat shock 70kD protein 6 (HSP70B′)	3310	X
7	*HSPA7*[a]	HSPA7	Heat shock 70kD protein 7	3311	X
8	*HSPA8*	HSPA8	HSC70; HSC71; HSP71; HSP73	3312	15481
9	*HSPA9*	HSPA9	GRP75; HSPA9B; MOT; MOT2; PBP74; mot-2	3313	15526
10	*HSPA12A*	HSPA12A	FLJ13874; KIAA0417	259217	73442
11	*HSPA12B*	HSPA12B	RP23-32L15.1; 2700081N06Rik	116835	72630
12	*HSPA13*[b]	HSPA13	Stch	6782	110920
13	*HSPA14*	HSPA14	HSP70-4; HSP70L1; MGC131990	51182	50497
HSP H					
1	*HSPH1*	HSPH1	HSP105	10808	15505
2	*HSPH2*[b]	HSPH2	HSPA4; APG-2; HSP110	3308	15525
3	*HSPH3*[b]	HSPH3	HSPA4L; APG-1	22824	18415
4	*HSPH4*[b]	HSPH4	HYOU1/Grp170; ORP150; HSP12A	10525	12282

Fig. 1. HSP70 family classification [20]
Рис. 1. Классификация семейства HSP70 [20]

release often involves the hydrolysis of ATP. The formation of functional complexes is not related to certain consensus amino acid sequences in the substrate protein, but rather is determined by the location of hydrophobic residues and conserved recognition sites [14, 43]. The researchers understood that a single chaperone would not provide stable work to maintain proteostasis. That is why, at the turn of the century, the identification of various adapter proteins, transport proteins, and signaling molecules in combination with chaperones also began.

The term "chaperome" was introduced in 2006 to denote a combination of chaperones, co-chaperones, and related factors [41]. The initial list of the human chaperome was published in 2013, and it reported 147 bioinformatically predicted members [13]. It included members of heat shock protein 90 (HSP90), HSP70, HSP60, HSP110, HSP40 (also known as DNAJ proteins), HSP10 and small HSP (sHsp), as well as their co-chaperones and participants of folding, the enzymes peptidyl-prolyl-isomerase (PPI) and protein disulfide isomerase. The name of each HSP family comes from the molecular weight of the original founding member and follows the current nomenclature. In eukaryotes, most families also include components specific to organelles, such as those expressed in the endoplasmic reticulum and mitochondria. Later studies expanded the list to 332 chaperones and co-chaperones, represented by 88 chaperones (27%), 50 of which were ATP-dependent, and 244 co-chaperones (73%) [2, 3]. Several proteins containing tetratricopeptide repeats (TPR) domain were also included based on their functional interactions with selected chaperones.

Analysis of protein expression in immortalized human cells (both in untransformed and cancer cells) identified chaperome components as some of the most common proteins in these cells [36]. HSP90 were the most common ones, accounting for an average of 2.8% and, together with HSP70, up to 5.5% of the total protein mass. Referring to the aforementioned database of 147 chaperome members, these proteins together account for 7.6% of the total number of polypeptides and 10.3% of the total protein mass in human cervical cancer cells HeLa. The chaperones HSP60 and HSP110 accounted for another 3.3% of the total protein mass, and 1.5% of the total mass consisted mainly of regulatory co-chaperone proteins for HSP90 and HSP70. More specifically, isoforms HSP90AA1 and HSP90AB1 (HSP90α and HSP90β) and two HSP70 proteins, constitutive HSPA8 (heat shock 70-related, HSC70) and heat shock-induced HSPA1A/B proteins represented the vast majority of chaperones of the corresponding families. In addition, all known HSP90 co-chaperones were substoichiometric with respect to HSP90. For example, the ratio of co-chaperone to HSP90 was 1:34 for AHA1, an activator of HSP90 ATPase activity, 1:46 for kinase-binding CDC37 [26], and 1:16 for HOP (HSP70-HSP90 adapter protein, also called STIP1, which binds HSP90 to HSP70) [5, 34]. Similarly, the ratio of co-chaperones to HSP70 was 1:5.5 for various J-domain co-chaperones that activate HSP70 to certain functions, and 1:7 for HSP110, which act as nucleotide exchange factors for HSP70 [10, 31].

These chaperones and co-chaperones are organized as interacting protein networks (Fig. 2). In eukaryotes, there are distinct and independent networks of chaperomes, with the main chaperone, such as HSP90 or HSP70, functioning with the help of a number of co-chaperones, each of which has a specific set of functions necessary for cell proteostasis. Not only RNA and ribosomes are involved in the synthesis of each protein, but also chaperome complexes characterized by close interconnection that can give the newly synthesized protein the topology required to perform its functions, and then send it to the appropriate cell compartment.

The chaperome is an extremely dynamic structure: HSP representatives included in it, the strength of bonds between proteins, and the functions performed depend on the state of the cell and its microenvironment. For example, studies of yeast cells have shown that Hsp82 is able to form stable networks with other chaperones during heat shock induction [19]. The accumulation of damaged proteins activates the expression of HSP110, which are able to "direct" HSP to the function of protecting and refolding protein aggregates [12]. Moreover, it has been found that constitutive and stress-induced forms of HSP70 and HSP90 are capable of forming functional oligomers in response to toxins or nutrient elimination [1, 27]. Thus, various manifestations of cellular stress can change the strength of interaction between both chaperone members and individual complexes. This reorganization of a higher order than the chaperone-substrate can lead to the emergence of new functions that are not normally expressed, but which may be required to counteract stress factors. It is worth noting that the same feature can maintain cell viability in case of a pathology.

It is known that chaperone complexes with high interaction strength are characteristic of tumor cells. Since the 2000s, researchers have been actively identifying and describing HSP70/90/110 complexes with AHA, JAK, BAG, HOP, BiP, and others in solid and hematological tumor cells [8, 21, 24, 25]. Unlike more dynamic complexes of normal cells, chaperomes isolated from tumors remain stable during in vitro studies. The inclusion of chaperome components in such stable complexes does not depend on the level of tissue expression, origin, or genetic mutations [6, 32]. Moreover, it was found that, despite their activity, such HSP complexes represent only a small part of the chaperome of a tumor cell, and not all isolated cultures are able to express them, which may serve as a basis for di-

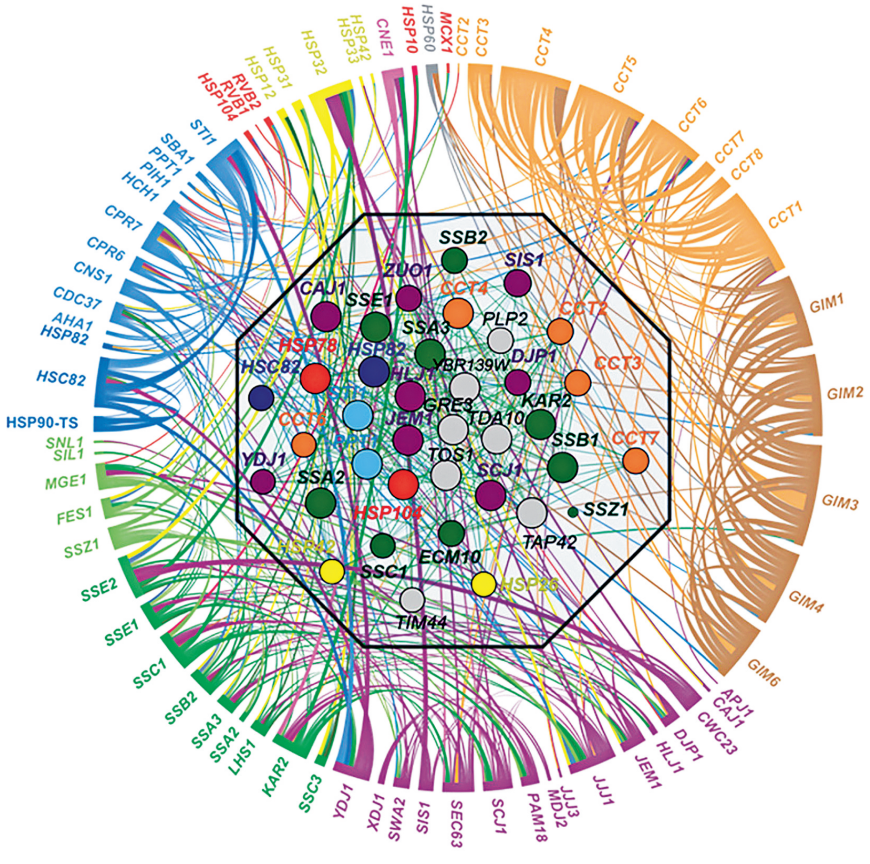

Fig. 2. An example of chaperome obtained via immunoassays and bioinformatic analysis [33]
Рис. 2. Пример шаперома, полученного иммуноферментным и биоинформатическим анализом [33]

viding cancer cell cultures into two types. Cancer cells require the formation of stable protein networks and maintenance of proteostasis. The chaperome is the main platform supporting the synthesis, organization, and protection of polypeptide pathways, also mediating signaling, transport, and intercellular contact [26, 35, 39]. This set of functions places the chaperone in the central position of the protein network, surrounding it with lower-order protein complexes and auxiliary molecules. This location is important in the diagnosis and treatment of cancer and opens up a chaperomic approach in personalized medicine: labeling or inhibiting the HSP protein knot with a high degree of connectivity is more likely to lead to the detection or apoptosis of cancer cells than targeting individual chaperones or dynamic complexes. It is this integrated approach that guides modern chaperome research both in the framework of cell biology and cancer theranostics.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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