The chaperonopathies
A new field of medicine for study by physicians and all others involved in medical sciences and public health

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Proteins are very important components of our body. They have a multitude of functions, but cannot work if they do not have the correct composition and shape. To achieve the latter, most proteins need assistance from other proteins called molecular chaperones. Molecular chaperones, chaperones in short, also called heat shock proteins or HSP, play key roles in health and disease, particularly as part of anti-stress mechanisms. Typically, HSP help other proteins to mature so they can achieve a final physiological shape and be useful to the cell. Briefly, chaperones assist other protein molecules from the moment they are synthesised inside a cell as they go through a series of folding steps until they reach a fully functional conformation. In addition to this participation in shaping growing molecules, chaperones also have other functions pertaining to protein quality control. For example, chaperones play a role in a) refolding partially unfolded proteins (as for example when they are damaged by stress); b) translocating newly formed proteins from their place of origin to their final destination (i.e. the location at which they will work); and c) eliminating proteins damaged beyond repair that are no longer useful. But the story does not end here. Chaperones have further functions inside and outside cells that are unrelated to protein quality control, for example, extracellular chaperones can act as signaling molecules for the immune system.

The wide range of different functions that chaperones can display is reflected in their variety. There are several types of chaperones, each type encompassing subtypes residing in various locations inside the cell and within a multicellular organism such as the human body [Table 1]. It is noteworthy that despite this variety, chaperones play a role in a) refolding partially unfolded proteins (as for example when they are damaged by stress), b) translocating newly formed proteins from their place of origin to their final destination (i.e. the location at which they will work), and c) eliminating proteins damaged beyond repair that are no longer useful. But the story does not end here. Chaperones have further functions inside and outside cells that are unrelated to protein quality control, for example, extracellular chaperones can act as signaling molecules for the immune system.

Abstract

CHAPERONOPATHIEN: EIN NEUES MEDIZINISCHES FACH FÜR ÄRZTE UND ALLE EXPERTEN IM BEREICH DER MEDIZIN UND DER ÖFFENTLICHEN GESUNDHEIT

Chaperones have been studied since the 1960s but it is only in the last decade or so that they have received significant attention from many scientists. However, they are still somewhat of a mystery to practitioners, physicians and other health workers, and also to a good proportion of biologists, health scientists, and teachers. This is mostly because the diseases due to chaperone failure have been classified and organised into a defined set of pathological conditions with unifying features only a few years ago, and because there is no systematic treatment of them in textbooks with only a few exceptions, for example the Encyclopedia of Stress. Likewise, these diseases have not been the theme of specialised symposia at scientific meetings, with one exception (www.umbi.umd.edu/computing/rss/player.php?id=884).

This lack of a unifying view has made it difficult for medical students and doctors to understand diseases caused by chaperone malfunction, in contrast to other pathologies, for example, diseases of the heart, diseases of the liver, diseases of the hematopoetic system, etc., which are clearly defined and described as units of learning in specialised books or chapters in textbooks, and are discussed in specialised symposia.

Along with my collaborator Everly Conway de Macario, I have been working on a systematic grouping and classification of pathological conditions due to chaperone malfunction over the last few years and have assembled them under the name chaperonopathies. They constitute a new field, or chapter, of Medicine, including Physiology, Medicinal Chemistry, Pathology, Pharmacology and Therapeutics, and all other specialties dealing with patients and related specimens used for diagnosis and other laboratory analyses.

In order to better understand the chaperonopathies it is helpful to comprehend the concept of chaperoning system. This, we propose, is a physiological system, like the immune and the hematopoetic systems, for example. The chaperoning system is constituted of the various groups of molecular chaperones that originate inside cells, some remaining there and others leaving them to gain the extracellular space and the lymph, blood, and other biological fluids [Table 1].

It can easily be realised that chaperones are everywhere in the organism and this clearly advertises the physiological importance of the chaperoning system. It follows that if one or more chaperones are defective the consequences will most likely be widespread and serious. The problem is that physicians and other health-related workers, including those involved in laboratory and field activities are not aware of this threat to the well-being of humans (and, of course of animals, too). Therefore, chaperonopathies are not taken into account when clinicians and pathologists study patients and biological samples from them. The chaperonopathies go undiagnosed, and are actually misdiagnosed most of the time. The consequences for the patient and for public health in general cannot be disastrous. The situation must be remedied immediately to avoid suffering, misguided treatments, and waste of money and other resources.

As mentioned above, we have undertaken the task of assembling the known chaperonopathies into a coherent group, including many diseases which are still under scrutiny and need to be studied more before they can be certified as belonging to this category. This is an emerging, growing field.

Classification of chaperonopathies into a defined field facilitates teaching and, consequently, promotes learning among medical and health science students at all levels, undergraduate, graduate, and post-graduate. Needless to say, this newly recognised group of diseases should also be introduced to pre-college students and the public at large. The consequences of this dissemination of knowledge will have a positive impact on multiple fronts, for example, I) it will increase the diagnostic capabilities of clinicians, pathologists, and laboratory personnel; II) as a direct consequence of the better diagnostic results, treatment (e.g. replacement chaperonotherapy) will be more specific and efficient; III) likewise, it will be possible to implement predictive (e.g., neonatal screening) and preventive (e.g. complementary chaperonotherapy) actions, which are not even considered now; and IV) it will enlighten administrators, politicians, and other public leaders concerned with public health, who allocate funds for research and health care, and will help them understand the reasons why they should also include in the high-priority range the study and management of chaperonopathies. In this regard, the Euro-Mediterranean Institute of Science and Technology (www.iemest.eu/web) is developing plans to organise courses and workshops on chaperonology, including the chaperonopathies and chaperonotherapy.

The chaperonopathies comprise a variety of pathological conditions and can be classified into genetic and acquired categories, depending on whether they are due to genetic defects (e.g. gene mutation) or post-genomic influences.
transcriptional-post-translational alterations (e.g. aberrant biochemical modifications occurring in the chaperones due to oxidation and other stressors during aging\(^9\)). All of them can, in principle, be approached therapeutically with chaperonotherapy by providing fresh, normal chaperones, gene or protein, to the diseased organism. However, chaperonotherapy is still in its beginnings and it will take a lot of more experimentation and clinical trials before it can be considered a routine procedure for various illnesses caused by defective chaperones.

Chaperonopathies can also be quantitative (if the affected chaperone is increased or decreased due, for example, to gene dysregulation) or qualitative if the malfunctioning chaperone has a structural defect, genetic or acquired, as described above.

A group of chaperonopathies is caused by normal chaperones that turn against the human body. For example, some chaperones are used by certain types of cancer cells to grow and proliferate and metastasize. In these types of tumors, normal chaperones inside the cancer cells contribute to malignancy. This is why these chaperonopathies have been named chaperonopathies by mistake or collaborationism, to indicate that a chaperone is helping the cell that causes disease. It was a collaborator with the enemy acting from within its own ranks\(^6,7\). In this case, chaperonotherapy should be aimed against the ‘mistaken’ chaperone and should cause its inhibition or elimination. This type of chaperone-targeted agents is being developed and constitutes a promising therapy for certain cancers, such as a group of breast tumors.

The need for funding for this very promising research emphasises the urgency of teaching chaperonology, including chaperonopathies, as mentioned above, not only to improve medical care and public health, but also to make fund-raisers and givers aware of this new area of Medicine and, thus, make them more sensitive to its needs.\(^6\)