Subject: Heat shock proteins & Metabolic disease

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December of 2015
Heat shock proteins (HSP):

are a family of proteins that are produced by cells in response to exposure to stressful conditions. They were first described in relation to heat shock, but are now known to also be expressed during other stresses including exposure to cold, UV light, and during wound healing or tissue remodeling. Many members of this group perform chaperone function by stabilizing new proteins to ensure correct folding or by helping to refold proteins that were damaged by the cell stress. This increase in expression is transcriptionally regulated. The dramatic upregulation of the heat shock proteins is a key part of the heat shock response and is induced primarily by heat shock factor (HSF). HSPs are found in virtually all living organisms, from bacteria to humans.

Heat-shock proteins are named according to their molecular weight. For example, Hsp60, Hsp70 and Hsp90 (the most widely-studied HSPs) refer to families of heat shock proteins on the order of 60, 70, and 90 kilodaltons in size, respectively. The small 8-kilodalton protein ubiquitin, which marks proteins for degradation, also has features of a heat shock protein.

Discovery:

It is known that rapid heat hardening can be elicited by a brief exposure of cells to sub-lethal high temperature, which in turn provides protection from subsequent and more severe temperature. In 1962, Italian geneticist Ferruccio Ritossa reported that heat and the metabolic uncoupler 2,4-dinitrophenol induced a characteristic pattern of puffing in the chromosomes of Drosophila. This discovery eventually led to the identification of the heat-shock proteins (HSP) or stress proteins whose expression these puffs represented. Increased synthesis of selected proteins in Drosophila cells following stresses such as heat shock was first reported in 1974.

Beginning in the mid-1960s, investigators recognized that many HSPs function as molecular chaperones and thus play a critical role in protein folding, intracellular trafficking of proteins, and coping with proteins denatured by heat and other stresses. Therefore, the study of stress proteins has undergone explosive growth.
Function

Upregulation in stress

Production of high levels of heat shock proteins can also be triggered by exposure to different kinds of environmental stress conditions, such as infection, inflammation, exercise, exposure of the cell to toxins (ethanol, arsenic, trace metals, and ultraviolet light, among many others), starvation, hypoxia (oxygen deprivation), nitrogen deficiency (in plants), or water deprivation. As a consequence, the heat shock proteins are also referred to as stress proteins and their upregulation is sometimes described more generally as part of the stress response.

The mechanism by which heat-shock (or other environmental stressors) activates the heat shock factor has been determined in bacteria. During heat stress, outer membrane proteins (OMPs) do not fold and cannot insert correctly into the outer membrane. They accumulate in the periplasmic space. These OMPs are detected by DegS, an inner membrane protease, that passes the signal through the membrane to the sigmaE transcription factor. However, some studies suggest that an increase in damaged or abnormal proteins brings HSPs into action.

Some bacterial heat shock proteins are upregulated via a mechanism involving RNA thermometers such as the FourU thermometer, ROSE element and the Hsp90 cis-regulatory element.

Role as chaperone

Several heat shock proteins function as intracellular chaperones for other proteins. They play an important role in protein-protein interactions such as folding and assisting in the establishment of proper protein conformation (shape) and prevention of unwanted protein aggregation. By helping to stabilize partially unfolded proteins, HSPs aid in transporting proteins across membranes within the cell.
Some members of the HSP family are expressed at low to moderate levels in all organisms because of their essential role in protein maintenance.

**Management**

Heat-shock proteins also occur under non-stressful conditions, simply "monitoring" the cell's proteins. Some examples of their role as "monitors" are that they carry old proteins to the cell's "recycling bin" (proteasome) and they help newly synthesised proteins fold properly.

These activities are part of a cell's own repair system, called the "cellular stress response" or the "heat-shock response".

**Cardiovascular**

Heat shock proteins appear to serve a significant cardiovascular role. Hsp90, hsp84, hsp70, hsp27, hsp20, and alpha B crystallin all have been reported as having roles in the cardiovasculature.

Hsp90 binds both endothelial nitric oxide synthase and soluble guanylate cyclase, which in turn are involved in vascular relaxation.

A kinase of the nitric oxide cell signalling pathway, protein kinase G, phosphorylates a small heat shock protein, hsp20. Hsp20 phosphorylation correlates well with smooth muscle relaxation and is one significant phosphoprotein involved in the process. Hsp20 appears significant in development of the smooth muscle phenotype during development. Hsp20 also serves a significant role in preventing platelet aggregation, cardiac myocyte function and prevention of apoptosis after ischemic injury, and skeletal muscle function and muscle insulin response.

Hsp27 is a major phosphoprotein during women's contractions. Hsp27 functions in small muscle migrations and appears to serve an integral role.
Immunity

Extracellular and membrane bound heat-shock proteins, especially Hsp70 are involved in binding antigens and presenting them to the immune system.

Clinical significance

Heat Shock Factor 1 (HSF1) is a transcription factor that is involved in the general maintenance and upregulation of Hsp70 protein expression. Recently it was discovered that HSF1 is a powerful multifaceted modifier of carcinogenesis. HSF1 knockout mice show significantly decreased incidence of skin tumor after topical application of DMBA (7,12-dimethylbenzanthracene), a mutagen. Moreover, HSF1 inhibition by a potent RNA aptamer attenuates mitogenic (MAPK) signaling and induces cancer cell apoptosis.

Applications

Cancer vaccine adjuvant

Given their role in antigen presentation, HSPs are useful as immunologic adjuvants in boosting the response to a vaccine. Furthermore, some researchers speculate that HSPs may be involved in binding protein fragments from dead malignant cells and presenting them to the immune system. Therefore, HSPs may be useful for increasing the effectiveness of cancer vaccines.
Metabolic disease:

Any of the diseases or disorders that disrupt normal metabolism, the process of converting food to energy on a cellular level. Thousands of enzymes participating in numerous interdependent metabolic pathways carry out this process. Metabolic diseases affect the ability of the cell to perform critical biochemical reactions that involve the processing or transport of proteins (amino acids), carbohydrates (sugars and starches), or lipids (fatty acids).

Metabolic diseases are typically hereditary, yet most persons affected by them may appear healthy for days, months, or even years. The onset of symptoms usually occurs when the body’s metabolism comes under stress—for example, after prolonged fasting or during a febrile illness. For some metabolic disorders, it is possible to obtain prenatal diagnostic screening. Such analysis usually is offered to families who have previously had a child with a metabolic disease or who are in a defined ethnic group. For example, testing for Tay-Sachs disease is relatively common in the Ashkenazi Jewish population. Countries that perform screening for metabolic diseases at birth typically test for up to 10 different conditions. Tandem mass-spectrometry is a new technology that allows for the detection of multiple abnormal metabolites almost simultaneously, making it possible to add approximately 30 disorders to the list of conditions for which newborns may be tested. If an infant is known to have a metabolic disorder soon after birth, appropriate therapy can be started early, which may result in a better prognosis. Some metabolic disorders respond very well if treatment is introduced at an early age. However, others have no effective therapy and cause severe problems, despite early diagnosis. In the future, gene therapy may prove successful in the treatment of some of these diseases.
The origins of metabolic disease

Metabolic pathways
In 1908 British physician Sir Archibald Garrod postulated that four inherited conditions of lifelong duration—alkaptonuria, pentosuria, albinism, and cystinuria—were caused by defects in specific biochemical pathways due to the diminished activity or complete lack of a given enzyme. He called these disorders “inborn errors of metabolism.” Although Garrod was incorrect in his categorization of cystinuria, his insights provided the field of biochemical genetics with a solid foundation, and the list of inherited inborn errors of metabolism has rapidly grown. This article is primarily concerned with these inherited metabolic diseases, although other disorders, including endocrine diseases (e.g., diabetes mellitus and hypothyroidism) and malnutrition (e.g., marasmus and kwashiorkor), also affect cellular metabolism.

Food is broken down in a series of steps by cellular enzymes (proteins that catalyze the conversion of compounds called substrates) into products with a different biochemical structure. These products then become the substrate for the next enzyme in a metabolic pathway. If an enzyme is missing or has diminished activity, the pathway becomes blocked, and the formation of the final product is deficient, resulting in disease. Low activity of an enzyme may result in the subsequent accumulation of the enzyme’s substrate, which may be toxic at high levels. In addition, minor metabolic pathways that usually lie dormant may be activated when a substrate accumulates, possibly forming atypical, potentially toxic, products. Each cell in the body contains thousands of metabolic pathways, all of which are interlinked to some extent,
so that a single blockage may affect numerous biochemical processes.
The consequences of metabolic imbalance may be severe; mental retardation, seizures, decreased muscle tone, organ failure, blindness, and deafness may occur, depending on which enzyme is dysfunctional. In recent years, it has become apparent that even some conditions associated with multiple congenital anomalies (e.g., Smith-Lemli-Opitz syndrome) have an underlying metabolic cause.

**Genetic mutations:**
The molecular blueprint for nearly all enzymes, structural proteins, cellular transport proteins, and other constituents that are responsible for carrying out the complex reactions involved in metabolism is stored as deoxyribonucleic acid (DNA) in the nucleus of the cell. A small amount of DNA of critical importance to metabolism also is contained in cellular organelles called mitochondria. DNA is organized into smaller units, termed genes, which direct the production of specific proteins or enzymes. In 1945 American geneticists George Beadle and Edward Tatum proposed a central tenet of molecular biology, the “one gene-one enzyme” principle, which states that a single gene directs the synthesis of a single enzyme. This principle has been refined to account for the fact that not all gene products are enzymes and that some enzymes are composed of multiple structural units encoded by different genes. Nevertheless, the one gene-one enzyme theory had immediate implications when applied to Garrod’s initial theories regarding inborn errors of metabolism. Inherited metabolic diseases were postulated to occur when a gene is mutated in such a way as to produce a defective enzyme with diminished or absent function. In 1948 methemoglobinuria became the first human genetic disease to be identified as being caused by an enzyme defect. In 1949 American chemist Linus Pauling and colleagues demonstrated that a mutation causes a structural alteration in a protein; hemoglobin (the protein in red blood cells that carries oxygen to the tissues of the body)
extracted from normal human red blood cells was shown to behave differently from hemoglobin taken from persons with the hereditary disease sickle-cell anemia. Thus, it was determined that mutant genes that direct the formation of abnormal proteins with altered function cause inborn errors of metabolism.