STRESS PROTEINS AND SIRS-SEPSIS
THE POSSIBLE ROLES OF HEAT SHOCK PROTEINS (HSP’S) IN THE DEVELOPMENT OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

Purnomo Suryohudoyo

INTRODUCTION

Systemic Inflammatory Response Syndrome (SIRS) was first recognized as a separate clinical entity when invading micro-organism which first caused a local inflammation overwhelmed our body’s defenses and began to invade the blood stream causing a much graver systemic condition, often endangering the patient’s life. It was then known variously as sepsis or septicaemia. When it became clear that the same systemic response could be elicited by other conditions other than microbial invasion a new term was coined: systemic inflammatory response syndrome (SIRS)

Heat Shock Proteins (HSP’s), also known as Stress Proteins are proteins widely expressed in both prokariotic and eukariotic cells. The fact that they are among the most phylogenetically conserved proteins suggests that they may somehow play a protective role to ensure cell’s survival against detrimental environmental insults

This short article was not intended to be exhaustive but may hopefully give the readers some general ideas on the possible role of HSP’s in the development of SIRS, more specifically SIRS of microbial origin (sepsis).

SIRS AND SEPSIS

Sepsis is SIRS of microbial origin. Thus the diagnosis of sepsis requires conformation that SIRS has a microbial origin. The symptoms of SIRS – Sepsis may be quite variable. However, the hallmarks of SIRS – Sepsis are: high fever, circulatory and multiple organ failure, ultimately leading to death.

Early sepsis is in most cases reversible, but if circulatory failure supervenes, characterized by hypotension and organ dysfunction (septic shock), the chance of the patient to survive the condition decreases substantially: many patients with septic shock eventually succumb despite aggressive therapy. Although many cases of sepsis are due to gram-negative and gram-positive bacteria accounting to the majority of cases, sepsis may occur in diseases caused by fungi, viruses, ricketsiae or protozoans.

Microbial blood-stream invasion as detected by positive blood culture may not always essential, because systemic spread of microbial signal molecules and toxins can also elicit the same response.

Sepsis is usually triggered when commensal micro-organisms spread from the gastro-intestinal, genitourinary and biliary tracts or from the skin and lungs. Localized infection in these organs may spread into the blood stream, often when the immune system of the patient is weakened, such that may occur in AIDS, elderly age, severe debilitating conditions, and the use of immune-suppressant drugs.

HEAT SHOCK PROTEINS (HSP’S)

The story of HSP began in 1962 with the discovery by Ritossa that subjecting Drosophila. melanogaster larvae to temperature shock resulted in a new pattern of chromosomal puffing in the fly’s giant salivary gland chromosomes, a sign of specific gene activation.

However, if was not until 1974 that the first products of these genes were identified when Tissieres demonstrated that the heat induced chromosomal puffing was accompanied by a high level expression of a unique set of proteins. The term: heat shock proteins was subsequently coined for these proteins.

It later turned out that HSP’s are not only induced by heat shock, but also by other cellular insults such as oxidative stress, uv radiation, exposure to certain chemicals (e.g. heavy metals), viral infection, ischemia etc. The common denominator of these different insults is that all are detrimental to cells’ survival. Thus the term HSP’s is somewhat a misnomer. A more
appropriate term would be Stress Proteins, alluding to the fact that these proteins are only expressed under stress, i.e. a condition detrimental to cells’ or organisms’ survival. The term heat shock proteins, however, persists in scientific literature.

Another fact that emerged was that certain HSP’s are expressed constitutively under normal, physiological condition but are upregulated during stress. HSP’s are categorized into several families that are named on the basis of their approximate molecular mass expressed in kilodaltons (kDa), e.g.: Hsp27, Hsp60, Hsp110 etc., but has its own name such as: BiP (binding protein) and Grp 94 (glucose regulated protein 94). These proteins are found in different cell compartments such as cytoplasm (Hsp90), mitochondria (Hsp60) and endoplasmic reticulum (Hsp 100). Some are alternatively located in two different compartments, e.g. Hsp70 (cytoplasm and nucleus). For a while, the exact function of HSP’s remains a mystery except that they must have some protective role since they are expressed in, and highly conserved between, both eukariotic and prokariotic organisms.

The first hint on what the function of HSP’s might be was the fact that the abovementioned environmental insults tend to damage proteins, thus the function of HSP’s must have something to do with restoring the functions of the damaged proteins. As it turned out, the function of the individual HSP appears to be quite various, but can be summarized and categorized into two general functions, i.e.

a. To maintain or ensure the correct structure (conformation) or location of a protein necessary for its proper function in vivo. This includes correct folding, disaggregation of abnormal protein aggregates, the induction or maintenance of active conformation and transport between two cellular compartments. Proteins exerting this function are called (molecular) chaperones, a special subclass of which are called chaperonins.

b. To destroy irreparably damaged proteins which will be of no use to the cells and may even interfere with normal cell functions. These are usually exerted by a special class of proteases (protein degrading enzymes) such as the ubiquitin dependent proteosome.

Knowing the function of HSP’s, it could now be easily understood why HSP’s are expressed during stress-full conditions. Also, we now know why some HSP’s are constitutively expressed in certain normal, physiological condition, especially in those conditions in which proteins are actively synthesized, such as during cell division, growth and differentiation.

Newly synthetized proteins are linear molecules that must be folded into its correct functional conformation. Also, some proteins are synthetized at a different location from that where it would exert its function, and thus have to be first transported to its proper location.

HSP’s gene transcription is mediated by the binding of a special group of transcription factors called: heat shock factors (HSF’s) to special sequences present within the heat shock gene promoter region called heat shock elements (HSE’s). When HSF binds to HSE, it then triggers the expression of HSP.

HSP1 is the principal heat shock factor in vertebrates. In the unstressed normal condition it is present in the cytoplasm in its inactive monomeric form, unable to bind DNA. Under stressful condition or under conditions in which proteins are actively synthesized, HSF1 is converted to the active phosphorylated trimer form by protein kinases which are members of the so called mitogen activated protein kinase (MAPK) pathway.

How the MAPK pathway became activated is not completely understood, but it is thought that it is activated by a flux of non-native proteins (proteins not present in its ‘usual’ functional form) caused either by damage or by increased protein synthesis. In its active phosphorylated trimer form, HSF1 is translocated into the nucleus and then binds DNA.

The generation of HSP’s has to be only transient, because the continued presence of HSP’s could adversely influence a variety of cellular functions. So there must be some way to stop the continued expression of HSP’s regardless of whether the stressful condition is still present or absent. This is accomplished by two mechanisms. One is by feedback inhibition, whereby Hsp70 whose expression is triggered by HSF, can inhibit the formation of active HSF1, and second, by binding of heat shock binding protein 1 (HSBP 1) to the active form of HSF1 which then prevent the active trimeric form of HSF to bind to the promoter region of the HSP gene.

THE HSP-SIRS /SEPSIS CONNECTION

HSP’s have been regarded as typically intracellular proteins, never found outside the cell except when the cell lyases or dies by necrosis, whereby its content is released into its surrounding.

This view is now proved not to be completely true. Although HSP’s can be found in the blood stream in several pathological conditions such as in myocardial injury and atherosclerosis which may be due to cell necrosis, certain HSP’s can be detected in sera of
clinically normal individuals. Also, certain in-vitro studies have found that HSP’s can be released from a variety of cultured human cells, such as islet cells, vascular smooth muscle cells and neuroblastoma cells.

It is thus clear, that HSP’s can be released from the interior of non-necrotic cells. The release of HSP’s did not appear to be mediated via the secretory pathways commonly used by secreted proteins. Instead, a selective, still unknown pathway may be involved. Certain HSP such as HSP60 and and HSP70 can act as an intercellular signaling molecules Bacterial and mycobacterial HSP’s can induce several cytokines including proinflammatory cytokines such as interleukin -1β (IL1β), interleukin 6 (IL 6) and tumor necrosis factor 1α (TNF 1α) from monocytes and macrophages. In addition, bacterial macrophages can induce human vascular endothelial cells to express adhesion molecules known to be involved in inflammatory reactions such as E-selectin, vascular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).

The fact that microbial HSP’s released into the blood stream, perhaps from necrotizing microbial cells, can induce pro-inflammatory molecules suggest that microbial HSP’s may contribute to the development of the systemic inflammatory response found in sepsis.

Certain human HSP’s, such as Hsp60 and Hsp70 can induce the same pro-inflammatory molecules as that induced by microbial HSP’s. Thus the possibility exists that self-HSP’s released from dying or stressed tissues’ cells during sepsis, may further augment the action of microbial HSP’s.

The fact that released self-HSP’s may have adverse effect seems to contradict the assumed protective role of HSP’s and brought into the question of what physiological role these released HSP’s could play. The identification of auto-antibodies against self-HSP’s in clinically normal individuals seemed to confirm the adverse effect of released self-HSP’s.

But every cloud has a silver lining. Released self-HSP’s may still have a protective role Evidence are accumulating that released self-HSP’s, acting as a signal molecule, could activate a subset of T lymphocytes called regulatory T-cells (T-reg). These are a recently discovered T-cell subset characterized by the expression of two surface molecules: CD4 and CD25 and is thus also known as T CD4+, CD25+ cells. These regulatory T cells are known to suppress the development of autoimmune diseases, allograft rejection and certain inflammatory diseases.

Investigators have long suspected the existence of lymphocytes able to suppress immune responses. They were thought to be T CD8+ cells. As it turned out now, they are in fact T CD4+ cells and the existence of the so-called T CD8+ suppressor cells has never been established.

CONCLUDING SUMMARY

Microbial HSP’s released during sepsis may contribute to the development of SIRS by inducing pro-inflammatory molecules. The action of microbial HSP’s can be further augmented by self-HSP’s. The adverse effect of released self-HSP’s is countered by the activation of T-reg, a subset of T-cells known to down-regulate inflammatory responses.

REFERENCES

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