Multi-author Reviews

Heat shock proteins

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Heat shock proteins. Introduction

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In 1962, Ritossa described in Experientia 'A new puffing pattern induced by temperature shock and DNP in *Drosophila*'[22]. Ritossa found, in the 2 L 14 and 15 regions of the giant chromosome from the salivary glands of *Drosophila bucksii* larvae, that some genes are activated whereas others are less active after an increase in the temperature from 25 to 30 °C for 30 min. In *Drosophila* these changes in gene activation are visible as the appearance or disappearance of so-called puffs (DNA unwinding on giant chromosomes). In 1974, the heat shock proteins (hsp) were purified from *Drosophila* by Tissierès and colleagues[18, 24].

It was already known at that time that exposure to chemicals could induce changes similar to those of heat shock[17]. These observations gave rise to numerous studies of the effects of various stresses on cells. Stress responses were detected ubiquitously in procaryotic as well as eucaryotic cells. Responses to stress can vary with the type of stress applied. Furthermore, the strength of any type of stress influences the quality of the stress response. For example, a heat shock response depends on the magnitude and duration of temperature elevation. Also, a heat shock of short duration prepares cells to cope better with a subsequent stress as compared to cells without a prior heat shock[17, 18].

One of the major heat shock proteins (see below) in bacteria is a predominant target for the immune response of mammals[27]. This is best illustrated by the fact that in immune responses to numerous bacteria an immunodominant, cross-reactive antibody response to these bacterial antigens was observed. The bacterial target antigen was therefore named "common antigen"[27]. "Common antigens" of bacteria have now been identified as heat shock proteins (hsp) with molecular weights of 58 to 65 kDa, all belonging to the hsp60 family, characterized by a high level of homology in their gene sequences. These findings were the basis for studies of the role of hsp in infection[27]. Analyses of immune responses during infection or after immunization with bacteria supported the view that bacterial hsp60 are also immunodominant antigens for cellular immune responses; the immune responses mediated by T lymphocytes (see contribution of Kaufmann[11]). Also, host hsp are expressed during bacterial infection (see contribution by Garbe[5]). The situation with respect to hsp during viral infection is different from that in bacterial infection. The viral genome does not code for hsp. However, marked expression of host hsp is observed during viral infection. Hsps even appear to play a role in viral replication, for example in the assembly of phage lambda[6].

When Cohen, Van Eden, and colleagues described in 1988 that mycobacterial hsp is involved in an experimental autoimmune disease called adjuvant arthritis in rats[25], hsp became candidates for being the causative antigens in arthritic diseases in humans as well, both in reactive and rheumatoid arthritis. Numerous reports appeared in the scientific literature describing reactions to (myco-)bacterial hsp of T cells obtained from patients with arthritis. However, in contrast to animal models of autoimmune diseases[4], a direct involvement of hsp in the human disease process has not yet been shown (see the contribution by Yang and Feige[26]). A marked expression of hsp in one of the target tissues, the cartilage, points to some regulatory events being influenced via hsp expression during the course of arthritis (for references see Yang and Feige[26]).

The immunodominance of hsp, and the existence of easily detectable immune reactions to autologous hsp, have led to various hypotheses about hsp: as 'a link between infections and autoimmune disease'[12]; hsp and the 'immunological homunculus'[1], and 'hsp: friend or foe?'[10].

Hsp are not only important in situations of heat shock or stress, where they were detected first and where their name originates, but also appear to be essential for cell survival in normal situations. One of the most prominent roles of hsp is in protein folding and degradation. This has led to the concept of hsp as chaperonins (a chaperone provides nursing or guidance)[3, 8]. For example, BiP (immunglobulin heavy chain binding protein) has been shown to be involved in immunoglobulin chain (anti-

body) assembly[9]. Ubiquitin, a member of another hsp family, binds to unfolded proteins which will then be degraded during protein turnover in cells[13]. Hsp70 is of importance during a stress response, for example in the prevention of protein aggregation, dissolution of protein aggregates, or in renaturation of denatured proteins[23]. Members of the hsp70 family contain an ATPase domain, and ATP hydrolysis is thought to be coupled to the release of substrate peptides[14]. Hsp have been shown to be involved in the process of antigen-presentation[19], during which an antigen is taken up by an antigen-presenting cell and processed (= cleaved), and fragments of the antigen are exposed on MHC (major histocompatibility complex) Class I or Class II molecules for presentation to T cells. This results in activation of those T cells which are specific for the antigenic epitope presented. It is noteworthy that the gene for human hsp70 is located within the MHC[7]. Involvement of hsp70 in antigen presentation is another example which illustrates that hsp have a role in cells normally, as well as in situations of stress.

Inflammation as a cause or a consequence of the immune reaction to self-components in autoimmune diseases is an issue that is often discussed. A recent review describes the role of hsp from the point of view of inflammation[20]. Steroids are widely used for the treatment of inflammatory reactions, so it is of interest that hsp90 bind to steroid hormone receptors[21]. In this context it is important to mention a hypothesis of hsp as "the missing link between hormonal and reproductive factors and rheumatoid arthritis"[2].

The aim of this series of articles is to view hsp as targets for the immune system and to examine the role of hsp in autoimmune disease and immune regulation. In addition, we felt it was timely to ask Alfred Tissières and his colleagues to give a view of the development of the field, and a historical perspective after 3 decades of hsp research[18]. Morange and colleagues describe the arrangement of hsp into families, their expression and functions[15]. Garbe focuses on the stress situation during infection; a stress for the invading microbe as well as for the host[5]. The immune system has to distinguish efficiently between foreign and self. How does the immune system fulfil this task when, in a situation of stress, such as infection, proteins are produced by both the invading bacterium and the 'defending' host which are highly homologous? What do T cells see ? What do B cells see? This is dealt with in the contributions by Kaufmann[11] and Mollenhauer and Schulmeister[16]. They summarize observations of situations where immune responses to hsp are easily detected in health and disease. The present series is rounded off by Yang and Feige reviewing the clear-cut involvement of members of the hsp60 family in various animal (models of) autoimmune diseases – in contrast to the continuing lack of convincing data showing a similar involvement of hsp in human disease[26].

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