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Multi-author Review

Developmental control of heat shock and chaperone gene expression*

Introduction

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Since the induction of puffs by a hyperthermic treatment was first described in EXPERIENTIA more than 30 years ago by the Italian geneticist Ferruccio Ritossa [1], the cellular heat shock response has attracted the interest of an increasing number of specialists from very different disciplines. It was progressively discovered that the proteins induced during the stress response, the heat shock proteins (HSPs), are generally present in every cell in the absence of stress, have been thoroughly conserved during evolution and play fundamental roles in protein folding and degradation in the normal cell. This accumulation of data placed these proteins high on biologists' agendas, at the interface between molecular biology, cell biology and physicochemistry.

The potential role of these proteins in the immune response, their involvement in inflammatory phenomena and their differential expression during cell transformation made them familiar to immunologists [2]. One domain of research which has not yet attracted sufficient attention from biologists is the developmental control of heat shock gene expression. Before their functions were unveiled, and even before they were nicknamed, the differential expression of HSPs during development and cell differentiation had already been described. As will be made explicit in the different contributions to this multi-author review, these observations concern both the constitutive and inducible expression of these proteins. These diverse data obtained mainly from *Drosophila*, *Xenopus* or mammals (mouse), as well as new data obtained recently, have not yet been reinterpreted in the light of the clues we now have to the function of HSPs and the mechanisms controlling their expression. The aim of this multiauthor review is to evaluate the functional significance of and to describe the mechanisms specifically involved in developmental control of HSP and chaperone synthesis. We intend to expand upon previous reviews published four years ago which were limited by the fragmentary information then available on HSP function and the mechanisms of heat shock gene expression [3]. This review will be published into two successive issues of *CMLS*, one devoted to nonmammals, the second to mammals (mouse).

Our strategy will be to compare the expression of HSPs and the mechanisms regulating this expression in different organisms. R. Tanguay's group will demonstrate that in *Drosophila*, an organism tightly linked with HSPs since their discovery, we have one of the most complete descriptions of HSP expression patterns and the mechanisms involved. Although a complete description is currently impossible, much information has also been obtained on the mouse. Four contributions will be devoted to the expression of HSPs during mouse (or rat) development. Two of these, on the whole embryo, will collect current information on HSPs and their regulation during zygotic genome activation (E. Christians et al.) and later phases of development (M. T. Loones et al.). Two contributions, from K. D. Sarge's and D. Walsh's groups, will focus on the involvement of HSPs in specific processes of differentiation and development, in spermatogenesis and during neural tube closure at the early phase of development. At least for the first of these two phenomena, the abundance of studies which have so far been performed reflects the complexity of HSP expression during this process. The reason for this remains obscure. Perhaps other differentiation systems also involve a very precise pattern of HSP expression but have not yet attracted the interest of experimenters. The very specific expression of HSPs during spermatogenesis might also be correlated with the extensive modifications in gene expression and cell structure occurring during this process. There is also a specific reason to look very closely at the expression of HSPs during neural tube closure. It is a very critical phase of development, whose perturbations lead to many (most) teratologic malformations observed in mammals (humans). The focus on this developmental system is a preferred way to verify the protective role of HSPs during development.

'Between' *Drosophila* and mammals, two reviews will be devoted to *Xenopus* (by J. J. Heikkila et al.) and ze-

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* This Multi-author Review consists of two parts:
Part I. Plants and nonmammals (this issue).
Part II. Mammals (will be published in the next issue of CMLS, Vol. 53, 2 (Feb. 97).

brafish (by P. H. Krone et al.). These organisms are intermediary, as far as our knowledge of HSPs and their regulation is concerned. Whereas there is only one heat shock transcription factor (HSF) in *Drosophila*, and three to four in mammals, the existence of different forms of HSFs has only recently been demonstrated in amphibians. The description of the main heat shock genes is not as advanced in these organisms as it is in *Drosophila* or in the mouse. However, studies on amphibians have already contributed much information on the mechanisms controlling heat shock gene expression during the first phases of embryogenesis. Moreover, these two systems are potentially very important because they provide the opportunity to control the level of HSP expression and to correlate expression of HSPs and developmental genes.

We have not included in this review the results obtained in *Caenorhabditis elegans* or another amphibian (*Pleurodeles*), nor the abundant data obtained in different in vitro differentiation systems. However, these data will be referred to by many contributors. It must be added that the differential expression of HSPs in the adult tissues of multicellular organisms is clearly related to the developmental control of heat shock gene expression. We have not specifically focussed our attention on these data, but they will be cited when pertinent by the different contributors. This review also does not consider variations in HSP expression during ageing. The data are complex and deserve a full study in themselves. It remains to be established that these variations constitute a final stage in the developmental programme of HSP expression.

Finally, one contribution will be also devoted to the developmental control of heat shock gene expression in plants, which will be presented by L. Nover and K.-D. Scharf. The properties of HSPs and their regulation here are different from those observed in the animal kingdom: the diversity of HSPs appears greater, in particular for the small heat shock protein subfamily, and plants are the only eukaryotic living beings where some of the HSFs regulating the expression of heat shock genes are themselves HSPs. However, plants are very important for the heat shock ‘field’ and for the purpose of our review. The ‘physiological’ significance of a heat shock response is obvious, and the data, altogether still too scarce, suggest a very complex differential expression of HSPs during development. This contribution has been placed at the beginning of this review, since its authors will also introduce basic information on the main characteristics of HSPs and HSFs, intended for the nonspecialist reader unfamiliar with the heat shock ‘jungle’.

We are conscious of the limitations of such a comparison between different organisms. Even if HSPs are expressed following a large number of stresses, distinct from the heat shock, and even if they play fundamental roles at ‘normal’ temperatures, it remains obvious that the control of their expression is not independent of the fact that the organisms harbouring them are poikilothermic or homoithermic. The very original study of K.-D. Sarge and K. E. Cullen (in this review) on the modifications of the heat-shock response of spermatogenic cells (but not of somatic testis cells) illustrates the complex link between the temperature (of cells and organisms) and the onset of the heat shock response. Moreover, the molecular mechanisms involved in development and differentiation in the different organisms are not similar, preventing an immediate comparison between data. Nevertheless, some interesting parallels appear in the different contributions. As the reader will discover, despite recent progress in the description of the ‘chaperone machinery’ [4], the main limitation to our present knowledge still lies in the paucity of data on the physiological functions of HSPs inside the cell.

1 Ritossa F. (1962) A new puffing pattern induced by temperature shock and DNP in *Drosophila*, Experientia **18:** 571–573
2 Feige U. and Mollenhauer J. (eds) (1992) Multi-author reviews on heat shock proteins. Experientia **48:** 621–656
3 Heikkila J. J. (ed.) (1993) Heat shock gene expression and development. Dev. Genet. **14:** 1–158
4 Hartl F. U. (1996) Molecular chaperones in cellular protein folding. Nature **381:** 571–580