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Heat Shock Proteins in Disease – From Molecular Mechanisms to Therapeutics

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This special issue is dedicated to the two main molecular chaperone families in human cells, heat shock protein 90 (HSP90) and HSP70. Long recognized for their importance as targets in a variety of human disease, these chaperone proteins have attracted strong interest from both academia and industry. The nine review articles included in this issue give an overview on the biology of these HSPs in disease, detail efforts dedicated to the discovery and development of small molecules to modulate HSPs with a therapeutic outcome in mind, and lastly, discuss why molecular chaperones are not typical targets and how this realization should change how we develop and implement HSP inhibitors for disease treatment.

In addition to an overview of the two HSP families, the issue will also focus on HSP90 and HSP70 paralogs. The HSP90 family of chaperones for example, has four major paralogs; of these, HSP90α and HSP90β are majorly cytosolic proteins, whereas GRP94 (glucose regulated protein 94) is mainly found in the endoplasmic reticulum (ER) and TRAP-1 (tumor necrosis receptor-associated protein 1) is found in the mitochondria. Similarly, the HSP70 family is comprised of cytosolic (HSP70 and HSC70, inducible and constitutive members, respectively), ER (GRP78 or BIP) and mitochondrial (GRP75 or mortalin) paralogs. Knowledge on the contribution of specific paralogs to disease phenotypes has only recently started to crystallize and as we detail below, several articles in this issue provide a look into these advances.

The common theme of the issue is that HSPs are regulators of cellular adaptation to stress, and that this role provides a weakness of which HSP-directed therapies may take advantage of. This stress may come from an increased signaling and transcriptional activity such as it occurs in cancers, accumulation of toxic proteins such as in neurodegenerative diseases or the hostile environment of the mammalian host such as seen for filiarial nematodes. While cancer has been the focus of many previous review articles on the cytosolic HSP90, we have here the review from Ansa-Addo *et al*. detailing the mostly recent advances uncovering the role of GRP94 in cancers and other diseases, from Fontaine *et al*. and Inda *et al*. discussing the molecular basis for targeting of HSP70 and HSP90, respectively, in neurodegenerative diseases, from Woodford *et al*. focusing on targeting HSP90 in non-cancerous maladies, especially in pathogen-induced human disease (*i.e.* viral, fungal, and parasitic invaders) and from Devaney and Gillian providing an excellent overview of HSP90 in parasitic nematodes. In the latter, a role for HSP90 in facilitating the drug resistance phenotype in organisms as divergent as fungi and tumor cells is also presented. HSP paralog specificity and a role for paralog-specific agents in diseases is discussed by excellent reviews by Ansa-Addo *et al*. and

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by Gewirth, which focus on the HSP90 paralogs, and by Fontaine *et al.* which discusses such implications in targeting either of the HSC70 or HSP70 paralogs in neurodegenerative diseases.

An overview of HSP inhibitors used to dissect disease mechanisms, the pharmacophores that comprise the majority of these inhibitors and the structural basis for their inhibitory role is discussed in a number of review articles in this issue. For example, pan-HSP90 inhibitors are described by Woodford *et al.* and by Shrestha *et al.*, with focus on those chemotypes that ultimately translated to clinic as potential anti-cancer therapeutics. Inhibitors used to dissect the role of HSP90 and HSP70 in neurodegenerative diseases are the focus of the reviews by Inda *et al.* and Fontaine *et al.*, respectively. Shrestha and Young provide a global overview of the multitude of small molecules discovered to modulate the function of HSP70, whereas Li *et al.* provide an elegant discussion of HSP70 allosteric inhibitors. Lastly, the HSP90 paralog-selective chemotypes are introduced by Gewirth in a review article where he also surveys developments in structural analysis, compound screening, and structure-based design for HSP90 paralogs.

The structural complexity of the HSPs and the fine-tuning role conferred by co-chaperones and post-translational modifications on HSP activity and function are discussed by several excellent reviews in this issue. For example, Gewirth focuses on the structural diversity and flexibility observed among the four HSP90 paralogs to discuss how and why paralog specific inhibitors can de discovered and developed. Woodford *et al.* and Shrestha *et al.* on the other hand, discuss the complex regulation of HSP90 functions by co-chaperones and PTMs, and how this additional layer of structural and functional regulation provides new avenues for therapeutic intervention. A glimpse into a similar additional layer of complexity for HSP70 is provided in a review by Li *et al.*.

Finally, an excellent review by Shrestha *et al.* discusses how these layers of structural and functional complexity can be co-opted into the discovery and development of HSP drugs. HSPs are widely expressed proteins found in all cells, normal and under stress, and as we have learned to appreciate, it is the functional state of HSP90 in cancer that provides the therapeutic index needed for the clinical success of such agents. Agents that are directed towards HSP90 in cancer are in fact directed to HSP90 complexes; ramifications of this finding for medicinal chemistry, and how traditional paradigms of drug discovery and development do not necessarily apply towards the development of HSP90-targeted agents are well discussed in this review article. The sentiment of this review is echoed by Inda *et al.*, where a similar case is presented for neurodegenerative diseases, and by Devaney and Gillian, which provide an elegant discussion on how the use of HSP90 by nematodes depends on the environment these nematodes survive in.

All together, this issue is a must read for scientists interested in chaperones in disease, from biologists to chemists to clinicians, and I hope you enjoy it!

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