biomolecules

MDPI

Editorial

HSP70: From Signaling Mechanisms to Therapeutics

Kenia Pedrosa Nunes * and Amanda Almeida de Oliveira *,†

Department of Biomedical Engineering and Sciences, Florida Institute of Technology, Melbourne, FL 32901, USA
* Correspondence: knunes@fit.edu (K.P.N.); biosciamanda@gmail.com (A.A.d.O.)
† Current address: Department of Obstetrics & Gynaecology, University of Alberta, Edmonton, AB T6G 2S2, Canada.

Heat-shock proteins (HSPs) are primary stress responders that are vital to maintaining homeostasis [1]. HSP70 (also known as HSPA) is a family of highly preserved HSPs that exerts many biological functions in health and disease [2]. In humans, the HSP70 family encompasses 13 homologous genes, which are expressed in a tissue-dependent manner and occupy various intracellular (iHSP70) compartments, such as the cytosol, mitochondria, lysosomes, and nucleus [3]. Adding to the complexity of this field, HSP70 can be detected in the extracellular (eHSP70) space, acting as an endogenous stress sensor [4–7]. Therefore, current research in this field (HSP70) spans from the search for novel therapeutics to the exploitation of new biomarkers. In this sense, this Special Issue includes a set of original research/review articles that summarize recent discoveries relating HSP70 to various conditions, including hypertension [7], vascular dysfunction associated with aging [8], cancer [9–11], atherosclerotic cardiovascular disease [12], and COVID-19 [13].

As discussed by Rodriguez-Iturbe and colleagues, in hypertension, HSP70 exerts both chaperone and cytokine functions and may induce, depending on the context, tolerogenic anti-inflammatory reactivity or immunogenic and autoimmune reactivity [7]. Low-grade sterile inflammation is a hallmark of hypertension, caused by the activation of innate and adaptative immune mechanisms [6,7]. One of the critical details highlighted is that the HSP70-mediated stress within an individual, whether pro-inflammatory or anti-inflammatory, is crucial to determining the progression of or protection from hypertension [7]. Additionally, HSP70 has emerged as a critical participant in the vasculature [14] due to its interaction with calcium-handling mechanisms [15] in a sex-dependent manner [16]; it might also utilize alternative routes in order to influence the pathophysiology of vascular diseases, such as hypertension. In this context, de Oliveira and collaborators demonstrated that age-related alterations in HSP70 are associated with a reduction in vascular responses to adrenergic stimulation, and consequently, to the impairment of arterial function [8]; this may be a factor influencing vascular aging, and in some cases, present a link between aging and comorbidities, including hypertension.

There is a dichotomy between the compartmentalization of HSP70 and its biological actions, with iHSP70 playing protective roles and eHSP70 promoting cell/tissue damage [2,4]. To date, the literature supports that, in cardiovascular diseases and with regard to cardiovascular risk factors, diminished iHSP70 and increased eHSP70 have detrimental effects. These findings have prompted the search for ways to shift the balance towards higher iHSP70 levels. As discussed by Nagai and Kaji, levels of HSP70 may be enhanced in skeletal muscle via exercise or thermal stimulation [12]. In fact, the authors emphasize that thermal stimulation protects against insulin resistance, suppresses skeletal muscle atrophy, and has anti-apoptotic and anti-inflammatory actions, which are factors associated with atherosclerotic cardiovascular diseases. While brief, this review elucidates the issue of the thermal modulation of HSP70 as a tool with which to prevent cardiovascular complications. Expanding the contributions of HSP70, and in light of the COVID-19 pandemic, Russo and colleagues [13] reported that severe COVID-19 patients present elevated eHSP70 levels and an impaired heat-shock response capacity, which may have implications

Citation: Nunes, K.P.; de Oliveira, A.A. HSP70: From Signaling Mechanisms to Therapeutics. *Biomolecules* **2023**, *13*, 1141. https://doi.org/10.3390/biom13071141

Received: 12 July 2023
Accepted: 14 July 2023
Published: 17 July 2023

for disease severity, plus long-term effects regarding disease susceptibility; this highlights yet another exciting avenue for research.

HSP70 is also associated with a vast number of cancer types, and often, its overexpression is linked to a poor prognosis [17]. In this context, HSP70 acts as a chaperone molecule while also exerting a regulatory function in essential signaling pathways within the tumor microenvironment. Such roles justify the many ongoing clinical trials considering the possibility of HSP70-based monotherapy via HSP70 inhibitors or in combination with other drugs [10]. An elegant study by Safi and collaborators [9] propounded that the level of serum HSP72 is a possible biomarker for advanced lung cancer, as it might potentially enable lung cancer and metastatic disease to be distinguished between. Although this study remains to be validated in a larger cohort of patients, to obtain a foretelling signature that can be employed to screen for lung cancer, or any other cancer type, would be a milestone in this field. Despite extensive data characterizing HSP70 as an ally in cancer management being available and the positive effects when this protein is blocked being exhibited, to date, inhibitors for HPS70 are not available in clinical practice [11]. As discussed by Mouawad and colleagues, in the context of onco-hematological diseases (and potentially other cancer types), a major challenge is the off-target effects of HSP70 pharmacological modulators, as HSP70 is a pervasive protein exerting multiple functions across all human systems. Thus, inhibiting this protein without compromising healthy cells is paramount; however, currently, it is extremely challenging.

In essence, the HSP70 research field is vast, and fulfils the diverse set of articles included in this Special Issue; this reinforces the dynamism of HSP70, while providing an insight into the challenges involved in transferring HSP70 from the bench to the bedside. Nevertheless, we firmly believe that the above-mentioned articles enhance our understanding of HSP70-mediated processes in human diseases; this is accomplished by providing insights into knowledge gaps, and hopefully, devising directions for future research in the field.

Author Contributions: Both authors have made a substantial, direct, and intellectual contribution to this work. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the National Institutes of Health (DK-131511).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hu, C.; Yang, J.; Qi, Z.; Wu, H.; Wang, B.; Zou, F.; Mei, H.; Liu, J.; Wang, W.; Liu, Q. Heat Shock Proteins: Biological Functions, Pathological Roles, and Therapeutic Opportunities. *MedComm* **2022**, *3*, e161. [CrossRef] [PubMed]
2. De Oliveira, A.A.; Mendoza, V.O.; Rastogi, S.; Nunes, K.P. New Insights into the Role and Therapeutic Potential of HSP70 in Diabetes. *Pharmacol. Res.* **2022**, *178*, 106173. [CrossRef] [PubMed]
3. Kampinga, H.H.; Hageman, J.; Vos, M.J.; Kubota, H.; Tanguay, R.M.; Bruford, E.A.; Cheetham, M.E.; Chen, B.; Hightower, L.E. Guidelines for the Nomenclature of the Human Heat Shock Proteins. *Cell Stress Chaperones* **2009**, *14*, 105–111. [CrossRef] [PubMed]
4. Krause, M.; Heck, T.G.; Bittencourt, A.; Scomazzon, S.P.; Newsholme, P.; Curi, R.; Homem de Bittencourt, P.I. The Chaperone Balance Hypothesis: The Importance of the Extracellular to Intracellular HSP70 Ratio to Inflammation-Driven Type 2 Diabetes, the Effect of Exercise, and the Implications for Clinical Management. *Mediat. Inflamm.* **2015**, *2015*, 249205. [CrossRef] [PubMed]
5. De Oliveira, A.A.; Priviero, F.; Webb, R.C.; Nunes, K.P. Increased EHSP70-to-IHSP70 Ratio Disrupts Vascular Responses to Calcium and Activates the TLR4-MD2 Complex in Type 1 Diabetes. *Life Sci.* **2022**, *310*, 121079. [CrossRef] [PubMed]
6. Rodriguez-Iturbe, B.; Lanaspa, M.A.; Johnson, R.J. The Role of Autoimmune Reactivity Induced by Heat Shock Protein 70 in the Pathogenesis of Essential Hypertension. *Br. J. Pharmacol.* **2019**, *176*, 1829–1838. [CrossRef] [PubMed]
7. Rodriguez-Iturbe, B.; Johnson, R.J.; Sanchez-Lozada, L.G.; Pons, H. HSP70 and Primary Arterial Hypertension. *Biomolecules* **2023**, *13*, 272. [CrossRef] [PubMed]
8. De Oliveira, A.A.; Mendoza, V.O.; Priviero, F.; Webb, R.C.; Nunes, K.P. Age-Related Decline in Vascular Responses to Phenylephrine Is Associated with Reduced Levels of HSP70. *Biomolecules* **2022**, *12*, 1125. [CrossRef] [PubMed]
9. Safi, S.; Messner, L.; Kliebisch, M.; Eggert, L.; Ceylangil, C.; Lennartz, P.; Jefferies, B.; Klein, H.; Schirren, M.; Dommasch, M.; et al. Circulating Hsp70 Levels and the Immunophenotype of Peripheral Blood Lymphocytes as Potential Biomarkers for Advanced Lung Cancer and Therapy Failure after Surgery. *Biomolecules* **2023**, *13*, 874. [CrossRef] [PubMed]

10. Zhao, K.; Zhou, G.; Liu, Y.; Zhang, J.; Chen, Y.; Liu, L.; Zhang, G. HSP70 Family in Cancer: Signaling Mechanisms and Therapeutic Advances. *Biomolecules* **2023**, *13*, 601. [CrossRef] [PubMed]
11. Mouawad, N.; Capasso, G.; Ruggeri, E.; Martinello, L.; Severin, F.; Visentin, A.; Facco, M.; Trentin, L.; Frezzato, F. Is It Still Possible to Think about HSP70 as a Therapeutic Target in Onco-Hematological Diseases? *Biomolecules* **2023**, *13*, 604. [CrossRef] [PubMed]
12. Nagai, M.; Kaji, H. Thermal Effect on Heat Shock Protein 70 Family to Prevent Atherosclerotic Cardiovascular Disease. *Biomolecules* **2023**, *13*, 867. [CrossRef] [PubMed]
13. Borges Russo, M.K.; Kowalewski, L.S.; da Natividade, G.R.; de Lemos Muller, C.H.; Schroeder, H.T.; Bock, P.M.; Ayres, L.R.; Cardoso, B.U.; Zanotto, C.; Schein, J.T.; et al. Elevated Extracellular HSP72 and Blunted Heat Shock Response in Severe COVID-19 Patients. *Biomolecules* **2022**, *12*, 1374. [CrossRef] [PubMed]
14. De Oliveira, A.A.; Nunes, K.P. An Additional Physiological Role for HSP70: Assistance of Vascular Reactivity. *Life Sci.* **2020**, *256*, 117986. [CrossRef] [PubMed]
15. De Oliveira, A.A.; Priviero, F.; Tostes, R.C.; Webb, R.C.; Nunes, K.P. Dissecting the Interaction between HSP70 and Vascular Contraction: Role of Ca 2 + Handling Mechanisms. *Sci. Rep.* **2021**, *11*, 1420. [CrossRef] [PubMed]
16. De Oliveira, A.A.; Priviero, F.; Webb, R.C.; Nunes, K.P. Impaired HSP70 Expression in the Aorta of Female Rats: A Novel Insight into Sex-Specific Differences in Vascular Function. *Front. Physiol.* **2021**, *12*, 666696. [CrossRef] [PubMed]
17. Murphy, M.E. The HSP70 Family and Cancer. *Carcinogenesis* **2013**, *34*, 1181–1188. [CrossRef] [PubMed]