Editorial

Heat Shock Proteins in Cancer

The heat shock proteins (Hsps, also denoted stress proteins) constitute a superfamily of molecular chaperones that are induced in response to a wide variety of physiological and environmental insults, thus allowing cells to survive to lethal conditions. These proteins play a central role in the correct folding of stress-induced mis-folded proteins and have the ability to chaperone specific client proteins. The relationship between Hsps and cancer has its origin back in the seventies when a number of institutions gained experience in the use of hyperthermia as a therapeutic approach to treat superficial tumors. However, in spite of the high sensitivity of cancer cells to heat shock, the lack of efficiency of this approach resulted of the difficulty to physically heat-up cancer cells and because heat shock treated tumor cells became thermotolerant. It was then realized that thermotolerance was not only a consequence of the stress-induced expression of Hsps but resulted also of the intriguing property of a wide range of tumor cells to constitutively express a high level of these proteins. Hsps, which are usually associated with a poor prognosis, play essential roles in tumor growth and metastasis both by inhibiting apoptotic death pathways and by promoting autonomous cell proliferation and resistance to chemotherapy, radiotherapy and hyperthermia. It was then discovered that some tumor Hsps, such as Hsp70, have the surprising property to act as immunogenic molecules bearing tumor antigen once they are released from cancer cells. Hence, Hsps appear to have dichotomous effects, being required for tumor cell survival but conferring a hazard for cancer cells due to their immunogenic properties. This special edition of *Current Molecular Medicine* contains review articles on the complex role played by Hsps in cancer. Nine articles, written by experts in their respective field, have been selected to cover the deleterious effects mediated by HSF1 (Heat Shock Factor 1, the transcription factor responsible of Hsps expression), Hsp90 and small Hsps. The paradoxical aspects of tumor Hsp70 are then described, followed by articles dealing with the possibility to obtain Hsps based anti-cancer vaccines and describing the role of circulating Hsps towards the immune system.

HSF1 plays an extremely important role in tumorogenesis. The article by Calderwood provided an updated review about the functions of HSF1 in cancer. After a brief recall of the role of HSF1 in stress conditions, the author described the chronical activation or overexpression of HSF1 in a wide range of cancers and pointed to the essential role of this factor for multiple pathways of malignant transformation. Then, the author summarized the remarkable pleiotropy in the properties of HSF1 in cancer. In addition to stimulate Hsps expression that decreases programmed cell death and senescence, this factor allows the overexpression of mutated oncogenic proteins required to enhance tumor growth. Moreover, HSF1 can stimulate kinases activity, regulate energy metabolism, permit the development of polyploidy and be an inhibitor of transcription towards genes that oppose metastasis. Finally, the author suggested the potential use of inhibitors of HSF1 as novel anti-cancer drugs.

Hsp90 is a proeminent anti-cancer protein target. The discovery of Hsp90 inhibitors came to the stage about two decades ago. The article by Whitesell *et al.* provided an updated review of the progress that have been made in developing compounds that inhibit Hsp90 chaperone activity for the treatment of cancers. After a recall of the disappointingly modest effects induced by the the first-generation of inhibitors, the authors described that, in turn, these compounds have been invaluable in probing how Hsp90 supports the dramatic alterations in cellular physiology that constitute the malignant phenotype. The authors then suggested that the failure of the first-generation inhibitors could be intrinsic to the target itself. Finally, they proposed that the utilization of Hsp90 by cancer cells is probably a better target that would enhance the activity of other anticancer drugs while at the same time limiting the ability of cancers to adapt and evolve drug resistance. The net result of this strategy could be a less empiric development of more efficient inhibitors.

Intrinsic and extrinsic factors impact Hsp90 targeted therapy. The article by Alarcon *et al.* discussed how the tumor intrinsic and extrinsic factors can modulate the efficacy of small molecules engaging the Hsp90 chaperone machine. The authors first recalled the historical background regarding Hsp90 inhibitors and mentioned that, during the past eighteen years, seventeen molecules entered into clinical trial without achieving regulatory approval. These inhibitors have nevertheless been highly valuable to better understand the role of Hsp90 and its client proteins in cancer. Then, the authors gave a critical appraisal about the current Hsp90 inhibitors which, in spite of interacting exclusively with Hsp90, have indirect pleiotropic effects by causing degradation of over two hundred Hsp90-interacting client proteins. This impacts critical multiprotein complexes and can, paradoxically, cause transient activation of protein kinase clients that triggers signal transduction pathways that may interfere with the inhibitor

efficiency. Finally, the authors suggested that a picture is emerging in which the impact of Hsp90 inhibitors is shaped by the tumor intracellular and extracellular milieu.

The small heat shock protein HspB1 (Hsp27), a member of the small heat-shock proteins family, plays a major role in cancer. The article by Nagaraja *et al.* gave an updated review of the deleterous role of HspB1 in cancer, enlighted by the fact that its expression correlates with poor prognosis. They next described recent observations which point to the fact that HspB1 plays a dual role by promoting both cancer development by suppressing host anti-cancer response, such as apoptosis and senescence, and by facilitating the enhanced expression of metastastic genes. Next, they reviewed the highlights of the most recent findings and role of HspB1 in metastasis. The authors finally described recent therapeutic approaches based on RNAi-mediated depletion of HspB1.

HspB1 (Hsp27) bears tumorigenic and metastatic roles consequently of its interaction with oncogenic client proteins. The article by Arrigo and Gibert reviewed the dynamic phosphorylation and oligomerization of HspB1 that act as a sensor which, through reversible modifications, allows cells to adapt and/or mount a protective response. The authors next described the large number of HspB1 interacting partners that have already been described in the litterature as well as the already known changes in the structural organization that allow HspB1 to chaperone specific client proteins. The authors further reviewed this point by discussing their own results obtained using peptide aptamers that specifically interfere with the structural organization of HspB1 and decrease its anti-apoptotic and tumorigenic activities. The authors finally concluded that altering HspB1 structural organization and consequently its interaction with inappropriate pro-cancerous polypeptide partners could be a novel approach to abolish HspB1 tumorigenic activity.

Alpha-Crystallins are members of the small heat-shock proteins family that are deeply involved in tumorigenesis. The article by Chen *et al.* first recalled the current knowledge about the essential roles played by alphaA- and alphaB-Crystallin in maintaining normal cellular structure and physiology of both ocular and some non-ocular tissues. Then, the authors discussed recent studies that have revealed abnormal expressions and functions of both alphaA- and alphaB-crystallins in several types of tumors. They further discussed the intriguing observations which revealed that these proteins have different or even opposite functions during tumorigenesis. The authors finally discussed the diverse molecular mechanisms that have been proposed to explain the roles of alphaA- and alphaB-Crystallin in cell apoptosis, cell proliferation and tumor metastasis.

Heat shock proteins are essential anti-tumor polypeptides that play a major role in antigen processing and presentation. The article by Multhoff *et al.* first discussed how it is becoming progressively more evident that curative tumor therapy depends on the presence and maintenance of an intact immune system which has the capacity to elicit cytotoxic effector functions against circulating tumor cells and distant metastases. The authors next reviewed the intriguing observations which demonstrate that Hsps, such as Hsp70, are involved in antigen processing and presentation and can act as “danger signals” for the adaptive and innate immune systems. The authors finally summarized the current knowledge relating to the induction and manifestation of Hsps-related immunological responses that are pertinent to the development and maintenance of protective anti-tumor immunity.

Hsps are important regulators of the innate and adaptive immune responses that can be used as key anti-cancer vaccine adjuvants. The article by Ciocca *et al.* reviewed the recent results describing the ability of Hsps to bind and present tumor associated antigens to professional antigen presenting cells through MHC class I and class II molecules, leading to the activation of anti-tumor CD8+ and CD4+ T cells. Then, the authors discussed why Hsps are considered as important anti-cancer vaccine adjuvants and described the different delivery systems that induce cellular immune responses resulting in tumor rejection. Finally, the authors reviewed several clinical studies and described the most promising results that have been observed in patients treated with Hsp-based anticancer vaccines.

Extracellular Hsps have been described to function as endogenous immunomodulators for innate and adaptive immune responses. The article by Tamura *et al.* first summarized the evidences that Hsps are released into extracellular milieu and act as activators for innate immune responses through toll-like receptors. The authors further discussed recent studies which demonstrated that innate immune responses elicited by both endogenous and exogenous danger signals were spatially and temporally regulated and could be manipulated using Hsp90, thereby controlling the immune responses. The author finally discussed how spatiotemporal regulation of Hsp-

chaperoned molecules within antigen-presenting cells affects the antigen cross-presentation and innate immune responses and could lead to establish outstanding Hsp-based immunotherapy.

In summary, this special issue gives a general overview and describes specific advances of the role played by heat shock proteins in cancer cells. Furthermore, the readers will find the description of already existing as well as promising Hsps-based therapeutic approaches that may help to decrease the lethal outcome of some cancer pathologies.

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