Heat Shock Proteins in the Cancer Immunity: Comprehensive Review on Potential Chemotherapeutic Interventions

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Abstract

Cancer is still a major research concern due to increased cancer incidences with increased tumor heterogeneity. Although the present therapeutic approaches to target cancer biomarkers are encouraging, they have limitations due to differential sensitivity with respect to the type and grade of tumors. The most important limitation incur to the tumor communication with the host system. Heat shock proteins (Hsps) have been identified as potential pharmacological targets to combat cancer. Majority of studies performed in vitro suggest their contribution in oncogenic signal transduction with a curtailed quest of information on host communication in vivo. Hsps play significant role in innate as well as adaptive host immune response. We review Hsp mediated host communication with the tumor in alleviating the host immune response. We also review how Hsp-dependent and Hsp-independent chemotherapeutic strategies can be used to target tumors both in vitro as well as in vivo and describe potential mechanism of action of such drugs in treating cancers. Altogether, a comprehensive cross-talk between Hsps and tumor immunity is provided.

Keywords: Cancer; Tumor; Hsps; Adaptive immunity; Innate immunity

Introduction

Despite significant advancements in identifying the key mechanism to target cancer, the anticancer drug discovery yet suffers from a formidable increase in cancer incidences. Increased civilization is increasing the risk of cancer incidences while prolonged therapeutic interventions promoting drug resistant aggressive cancer phenotypes. Preclinical research studies using small molecule inhibitors have significantly contributed for innovative anticancer therapeutics, however, in the clinical perspective these studies have constraints due to (i) mononuclear infiltration, (ii) spontaneous regression, (iii) relapse, (iv) poor communication in case of immune deficient host system and (v) elevated antitumor immune response through tumor specific antigen interaction with the host immune system [1]. Therefore, strategies that promote enhanced host-tumor communication either through innate or adaptive mechanisms are thought to be attractive anticancer regimens.

Adaptive vs Innate Immune Signaling

The basal immune system arises either from myeloid progenitors or lymphoid progenitors. The myeloid progenitor cells (neutrophils, basophils, eosinophils, macrophages and dendritic cells) are majorly implicated in the activation of host innate immune response, which of late is considered to be the major tumor communication with the immune system. However, together with lymphoid progenitor cells (B-Lymphocytes, T-Lymphocytes and natural killer (NK) cells) these cells promote humoral response. The adaptive immunity is thought to be a complete defense mechanism compared to the innate immune system. Between the adaptive and innate immune responses, the adaptive immune response appears to be specific but a slow process that involves memory. Activated B- or T-cells can develop into memory cells. The adaptive immunity can be differentiated into, naturally acquired or active immunity that is stimulated by pathogen or antigen and artificially acquired or passive immunity activated by natural transfer of antibodies to another system or stimulation by the antiserum. Whereas the innate immunity is non-specific, constitutively present and shows immediate response, thus may or may not involve memory. Considering these differences, the immune system is being generally categorized as antibody-mediated (adaptive) system and cell-mediated (innate) system. Heat shock proteins (Hsps) act as macromolecular mediators for immune signaling both in adaptive as well as in innate immune responses, therefore are extensively studied for cancer immune signaling [2].

Hsps Act as Regulators of Immune Mediated Tumor Suppressor Mechanisms

Having chaperoning functions, Hsps play a central role in the maintenance of protein homeostasis, especially in the folding of nascent polypeptides, refolding of damaged or denatured polypeptides, in the trafficking of polypeptides to reach their cellular destinations and proteosomal degradation of irreversibly damaged proteins [3]. Civilization-associated diseases, including cancers, are the result of cellular adaptations to changes in the microenvironments aided by high expression of Hsps [4]. Cancer being a polygenic disease acquires high quality cellular adaptations to multiple cellular defects compared to their parental phenotypes. Induced expressions of different Hsps were conferred in promoting cell survival under severe stress conditions such as limited oxygen supply and enhanced proliferation stress. Despite differential expression patterns in different tumor cells, Hsps expression majorly contributes for evading normal cell death pathways, induced proliferation, and metastasis development, the most common characteristics of cancer cells [5]. Therefore, the expression profiles of Hsps can be indicative of grade and type of some tumors [6].

Hsp expression can also interfere with the host immunity due to

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their survival advantage on cancer cells [7]. The microenvironment responsiveness that directly activates specific gene expression patterns to decide the fate of cells is linked to the division potential. The host immune system comprises the most important tumor suppressor mechanisms in vivo. Although Hsps such as Hsp90 were promoting tumor formation bypassing the tumor suppressor systems, their involvement in immune modulation appears to be quite interesting. While intracellular Hsps are involved in antigen presentation to the immune systems, the extracellular Hsps act as danger signals promoting tumor immunogenicity. Hsps present antigenic peptides to class II MHC cells (also called as antigen presenting cells or APCs) and are found to be receptor independent because class II MHC bind antigens are extracellular and processed by the endocytic pathways [8]. Hsps also bind to class I MHC in a receptor dependent manner involving receptors like CD91 [9].

Hsps play a complex role in the mediation and maintenance of immune functions majorly in the transport, trimming and presentation of antigenic peptides to immune molecules [10,11]. Earlier studies have identified Hsps as activators of innate immune system [12], however, subsequent studies revealed that they also play major role in humoral immunity [13]. Conclusively, extracellular Hsps act as potent stimulators of class II MHC than the class I MHC molecules. Additional studies have revealed that Hsps, such as Hsp70, Hsp90 and gp96 are involved in cross-presentation of antigenic peptides to the class I MHC present on the surface of macrophages and dendritic cells [14]. It was also reported that tumor derived Hsp-peptides elicit enhanced tumor immunity compared to peptides presented to the immune system. Surprisingly, Hsps themselves are not potent activators of the immune system, but enhance antigen presentation upon their binding to antigenic peptides [15]. Interestingly, the surface or extracellularly expressed Hsps not only act as danger signals, but effectively elicit antitumor response through NK cells. Therefore, chemotherapeutic drug induced exosomes are considered to be the potent inducers of adaptive immunity [16]. A large variety of anticancer drugs (as reviewed in reference 16) were shown to induce tumor-derived exosomes.

Innate immunity is the first line of defense against a large variety of stresses [15], and thought to be the ancient form of defense in living beings [17,18]. In the following, we provide a comprehensive cross-talk between cancer cells and host innate immunity mediated by Hsps. As an exception, while some Hsp-based antigen presentation gained biological significance towards treatment strategies, Hsps such as Hsp60 promote cytokine production, thus, contribute to autoimmune diseases. Later it was found that not only Hsp60 but also gp96 is involved in such mechanisms, involving lipopolysaccharide (LPS) to elicit host defense through Toll-like receptor (TLR) signaling [15].

Neutrophils in the Innate Cancer Immunity

The myeloid lineage cells are majorly implicated in the innate immunity (non-specific immunity). The immune cells that are involved in the innate immunity are mobile, hence, can reach the tumor site by themselves. The major molecules in this class of immune cells are the neutrophils and macrophages that are known for their phagocytic functions. They are however, distinguished by the pyogenic function limited to neutrophils and not exhibited by macrophages. Since Hsp expression in both these cell types elicits effective antitumor response, they are linked to growth and spread of cancer. Neutrophils are frequently present on sites of tumor and promote tumor growth and invasiveness. The inflammatory responses can be produced by these tumor stimulated neutrophils through oxygen free radicals that in turn promote tumor growth. In contrast to the cancer, the pathogen-induced, dying neutrophils express Hsps to elicit macrophage response. Neutrophils mediate antibody-dependent cell cytotoxicity (ADCC) against tumor cells via Fc receptor (FcR) and subsequently lyse them. Impairment of neutrophil mediated ADCC suggests an important role for neutrophils in the tumor cell lysis. It has been shown that surface expressed Hsp70 interferes with the ADCC property of tumor cells. Pertinent to mention, among the numerous cell types within the tumor and its stroma, neutrophils have received less attention. Neutrophils express CD66a, CD66b, CD66c and CD66d receptors. The CD66 family of molecules associates with tyrosine kinase family of proteins that mediate neutrophil activated signals [19]. Since Hsp90 regulates src family of kinases [20], targeting protein kinases using Hsp90 inhibitors has been proposed as an efficient antitumor strategy [21]. Anticancer treatments such as radiotherapy and chemotherapy can reduce neutrophil number. The redundant neutrophil removal by selective apoptosis therefore appears to be beneficial in cancer treatment, however, over expression of Hsps can interfere with induced cell death pathways [22].

Macrophages in the Innate Cancer Immunity

The monocytes develop in the bone marrow and invade tissues as macrophages. Several specialized macrophages like Kupfer cells in the liver, sinus histiocytes in the spleen and lymph nodes, microglia in the neural tissue, epithelioid cells in the granulomas, dust cells/ alveolar macrophages in lungs, giant cells from connective tissue, and osteoclasts in the bone and peritoneal macrophages in the peritoneal cavity are known. However, the tumor activated macrophages (TAM, M2 type) play significant role in tumor angiogenesis and metastasis through inflammation mediated by tumor necrosis factor following Nfkb activation. Fully functional TAMs that infiltrate tumor tissues are further stimulated by either tumor derived or T-cell derived cytokines and activates adaptive immunity [23]. Therefore, TAM targeting has also emerged as an alternate strategy for solid tumors. Small heat shock protein family member, Hsp27 was shown to be involved in the macrophage differentiation from monocyte [24]. Hsp90 interacts with macrophage migration inhibitory factor (MIF), which is involved in cancer progression to metastasis. Breast cancers that are MIF positive were selectively targeted by anti-Hsp90 treatments through MIF destabilization [25]. The surface expressed Hsps can interact with CD14 macrophage receptors to induce pro-inflammatory response. Hsp60 activates APCs through CD14 and through p38 mitogen-activated protein kinase signaling sharing the intracellular signaling pathways activated by LPS. Constitutive expression of macrophage Hsps inhibits macrophage activation; however, pharmacological inhibition of Hsps alone is sufficient to inhibit macrophage activation in response to taxol or LPS [26]. In some experimental conditions, over expression of intracellular Hsps was found to interfere with ADCC property as well as TAM and peritoneal macrophage (PAM) activations [27]. Since TAMs can express a large variety of macrophage markers like, CD14, CD68, MAC387, CD163 and DAP12 that may play different roles in tumor immunity, further studies required especially to understand Hsp-dependent functions [28].

Basophils and Eosinophils in the Innate Cancer Immunity

The three major white blood cell populations, basophils, mast cells and eosinophils are present in the peripheral blood cells and...
are involved in immune signaling. While basophils and eosinophils are involved in the allergic responses, mast cells are implicated in tumor angiogenic response. Basophils respond to allergens through the production of IgE antibodies from B-cells independent of T-cells, whereas, eosinophils stimulate antigen presenting cells to produce antibodies. While the anti-inflammatory drugs can reduce eosinophils, Hsp90 is identified as a target for anti-inflammatory drugs suggesting Hsp90 involvement in the eosinophil mediated allergic responses. Basophils bind to FcεRI receptor and eosinophils bind to CD67 receptor and activate inflammatory responses. It was shown that neither of the receptors depends on Hsps, however, the intracellular signal transduction preceded by the ligand binding may require Hsps such as Hsp70 and Hsp90 for stress management and signal transduction respectively. Interestingly, the functional dependency of mast cells for Hsps is though limiting, majority of anti-inflammatory treatments using non-steroidal anti-inflammatory drugs (NSAID) induces Hsps, suggesting their role in cytoprotection under oxidative stress conditions [29].

**Dendritic cells in the Innate Cancer Immunity**

Dendritic cells (DCs) are antigen presenting cells (APCs) and also called as professional APCs. Similar to neutrophils, basophils and eosinophils, the dendritic cells also arise from CD34+ progenitor cells on stimulation with cytokines. Active DCs are the differentiated cells, which have the ability to take up antigens and present to MHC molecules, whereas mature DCs activate T-lymphocytes. Hsp production is not only linked to cytokine production, but also enhances the DC maturation and CD40, CD86 and CD83 expression. For this reason, decreased Hsp70 expression decreases the differentiation potential of DCs from monocytes [30]. Therefore, Hsps such as Hsp70, Hsp60 and gp96 are found to contribute for DC maturation, however, with varied response [31]. Hsp70 derived from DCs was shown to have potent anticancer immunity due to its involvement in the antigen presentation to the T-lymphocytes [32]. The COX2 NSAIDS inhibitors interfere with prostaglandin signaling and further promote DC-based vaccine immunity through Th1-polarized antitumor response and regress tumor in the host [51]. Interestingly, the Hsp70 bound DCs were found to exhibit enhanced Th1-polarized antitumor response and regress tumor in the host [51].

Hsps in the Cross-talk of Innate and Adaptive Cancer Immunity

The MHC molecules (Class I and Class II MHC molecules) are displayed on cell surface and recognize lymphocytes and APCs. Class I MHC molecules are present on all cell types and present antigens to CTLs (cytotoxic T-lymphocytes), whereas Class II MHC molecules present antigens to B-lymphocytes, macrophages and other APCs. Both MHC molecules and Hsps bind to peptides, however MHC molecules present antigenic peptides to immune cells, whereas Hsps present antigenic peptides to MHC molecules but not directly to immune molecules [47]. As detailed in the previous sections, DCs, NK cells and macrophages are the major immune molecules that are involved in both innate and adaptive immunity. While macrophages are implicated in carrying Hsp-bound antigenic peptides, DCs are having receptors such as CD91 for Hsps on their surfaces and these Hsps carry antigenic peptides from necrotic cells [48–50]. In support of this, the eosinome based Hsp70 appears to elicit the MHC-independent Th1-polarized antitumor response and regress tumor in the host [51]. Some of the antitumor drugs like the DNA damaging agents, cisplatin and doxorubicin can increase the eososome release [52,53], whereas cytotoxic drugs decrease eososome release [54] and the proton pump inhibitors and anticancer drug curcumin interfere with eososome release from tumor cells [55].

TLRs are transmembrane proteins containing Toll/ILR1 (TIR) motifs in the cytoplasmic domains [56] and exhibit varied sensitivity to different stimulators by isoform expressions. The extracellular Hsps, but not the intracellular Hsps, were shown to be the ligands for TLRs [3,57]. However, Hsp-mediated TLR signaling occurs by TLR2 and TLR4, whereas the surface expression of TLR1, TLR2 and TLR4 required gp96 [58,59]. Hsp60 can also activate macrophages through TLR4 [60] and TLR2 [61] despite its TLR-independent T-cell activation [62]. Although direct involvement of Hsp90 is not known for TLR signaling, its parologue, grp94 is involved in chaperoning of multiple TLRs [63]. We discussed about Hsps involvement in neutrophil, basophil, eosinophil and mast cell functions, and macrophage activations to release inflammatory cytokines contributing majorly to tumor progression, where TLR-independent functions are anticipated [64] and reviewed.
how Hsps are involved in the differentiation and maturation of dendritic cells and summarized Hsps role in TLR signaling [65].

The Hsp-bound antigenic peptide mediated cancer immunity had been widely accepted and popularized as a personalized cancer vaccine (http://www.agenusbio.com). However, in the recent past such approaches were shown to break immune tolerance through autoagression. For example, the mycobacterial Hsp60 based immunization induced (a) crossreactive CD8 α/β T cell receptors and (b) the T cells recognized Hsp60 peptides on MHC molecules in vitro and after transfer to α/β T cell-deficient mice induced autoimmune disease with severe damage to the gut epithelium [66]. However, the HSP60 chimeric DNA vaccines generated strong E6- or E7-specific immune responses and anti-tumor effects in vaccinated mice through cross-priming [67], further, DNA-Hsp65 vaccine has potent therapeutic and prophylactic effect against both tuberculosis and tumors [68]. While gp96 and Hsp60 based vaccination was demonstrated to be antigenic, a mixture of Hsp-derived peptides was shown to promote antitumor response to chemotherapeutic drugs [69]. The Hsp-derived peptides although elicit antitumor response it was limited to personalized treatment, hence demand for alternate strategies that can either sensitize or promote antitumor immune response for a large variety of tumors [70].

Hsps and Oxidative Stress in the Innate Immunity

Both inflammatory cytokines and reactive oxygen species (ROS) were shown to control innate immune responses. Neutrophils make use of ROS to interfere with pathogen infection by inducing the bactericidal activity [71]. The endogenous ROS produced may affect diverse cellular functions especially affecting the tyrosine kinase dependent signal transduction as well as NFκB pathways that are majorly implicated in cytokine or chemokine production [72]. Interestingly, the phagocyte induced ROS production is not involved in autoimmune disorders [73]. However, glutathione the intracellular antioxidant is known to control ROS production thus, controlling the inflammatory immune responses [74]. Decades of research on whether Hsps themselves act as antioxidants provided insights that Hsps are required to bypass or resist oxidative insults. It is known that ROS production can stimulate HSF1 activation which in turn activates Hsp synthesis, Hsp expression acts both antiapoptotic and anti inflammatory. Nitric oxide (NO) release by HSP-activated APC may also provide a layer of immunomodulation of Th cells by necrosis-released Hsps [22,75-77].

Localization Specific Functions of Hsps in Cancer Immunity

The cytosolic Hsps were attributed in antigen presentation to Class I MHC molecules (endogenous antigen presentation), whereas surface expressed Hsps are involved in antigen presentation to Class II MHC molecules (exogenous antigen presentation) [10]. Cyttoplasmic chaperone Hsp90 is in the centre of the foldosome complex machinery assisting both in protein folding and completion of folding [78]. Irreversibly damaged proteins are directed to proteasomal degradation; therefore, it is the site for antigenic peptide generation [79-81]. The ER chaperone grp94 or gp96 is also involved in chaperoning the antigenic peptides to immune molecules [82]. HSP-mediated antigen traffic towards proteasomal degradation is therefore coupled with acquired T cell immunity. Further, in the cytosol, only Hsp-chaperoned or Hsp-bound antigenic peptides are efficiently presented to the immune cells rather than free or Hsp-unbound antigenic peptides [83]. The cytosolic Hsp90 is also involved in the cytoplasmic translocation of antigens presented by the DCs through endosomal pathways [84-86]. The cytosolic Hsp70 members are implicated in direct shuttling of antigenic peptide processing and presentation [87,88] and tumor derived Hsp70-pulsed DCs show activation of immune response through CTLs [89].

The surface expressed Hsps send danger signals to the immune system and help in attraction and interaction of immune cells with the tumor cell. The binding of peptide-free HSP70 to APCs via TLRs initiates the secretion of pro-inflammatory cytokines and thus, results in a broad non-specific immunostimulation. An unusual membrane localization of Hsp70 on tumor cells acts as a tumor-specific recognition structure for NK cells [90]. Similarly, Hsp60 also enhances CD4+ and CD25+ T cell functions via TLR signaling [91]. Interestingly, extracellularly expressed Hsp90, by internalization is involved in the translocation of chaperoned antigen, its processing through endosomal or proteasomal processing to generate antigenic peptides [85]. The surface Hsps are either directed for their surface expression or released from virus-infected cells or tumor cells in vivo during lysis of cells during infection or by the action of antibodies or nonspecific effectors. The Hsps, which are now complexed with antigenic peptides derived from the cognate cells, are taken up by macrophages or other specialized antigen-presenting cells including CTLs, possibly by a receptor-mediated mechanism as discussed earlier [92].

The involvement of exosomes (nano-meter size vesicles secreted by live cells) in modulating the cellular immunity is a curtain raiser for additional functions of extracellular Hsps. Interestingly, although different Hsps are shown to be present in exosomes, Hsp70 and Hsp90 that are present in the lumen but not on the surface of exosome are attributed to the exosome mediated immune functions [93]. Exosomes also present antigenic peptides to DCs and are found to be somewhat selective for tumor peptides [94]. Further, B-cell exosomes also involve Hsps in the immune function stimulation [93].

Hsp Autoregulation: Negative Feedback and Chemotherapeutic Interventions

Induced Hsp synthesis is tightly regulated by heat shock transcriptional factor 1 (HSF1). The HSF1 is negatively regulated by Hsp90 or Hsp70 chaperone under normal physiological conditions. Stress activates HSF1 by disassociating the interaction between Hsps and HSF1. There are two mechanisms through which enforced HSF1 activation can be achieved, (i) disassociation of HSF1 from chaperones by inducing proteotoxic stress and using direct inhibitors of Hsp90, or (ii) direct activation by NsAIDS like sodium salicylate, indometahcin and aspirin, and drugs like geranylgerany acetone, rabapimide, carbenoxolone, paloprezinc, celestrol, paeonoflorin, glycyrrhizin, curcumin. Co-inducers like bimoclomol and BRX-220 can also induce Hsp gene transcription through HSF1 activation. These findings therefore, suggest that targeting HSF1 in tumor cells can target stress response and may elicit antitumor response [95].

Although direct information related to HSF1 and cancer immunity is scarce, using experimental animal models it has been demonstrated that HSF1 is involved in multipathogenesis defense pathways in eliciting the host immune response [96]. However, HSF1 independent immune-modulation of Hsps in DC maturation in hsf1/- knockout mice suggests involvement of alternate factors in Hsp synthesis and maintenance [97]. In contrast to the classical hypothesis, that only HSF1 is involved in the induced transcription of heat shock geneses, particularly in cancers, induced activation of HSF2 was also reported.
While Hsp expression elicits antitumor response in the host immune system, Hsp expression in tumor cells helps to evade the host immune attack (Figure 1). The chemotherapeutic interventions using rituximab, trastuzumab, alemtuzumab, catatumumab etc were known for inducing the ADCC, CDC and apoptotic processes. The personalized antibodies such as zalutumumab, panitumumab and nicmotuzumab were also known to induce ADCC of target cells. Several FDA approved current monoclonal antibodies used in the current cancer therapy can sensitize tumor lymphocytes to CDC [77]. In subsequent studies, it was demonstrated that this activity is not specific to lymphoid cancer, but also applicable to solid tumors [101].

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Since tumors are considered the potential targets for innate immunotherapy, stimulation of NK cells using chemotherapeutic approaches can be of particular interest. The chemotherapeutic drugs, 5-FU, Ara-C, cisplatin and radiation therapy targeting the DNA damage pathway can increase the expression of NK cell stimulating ligand, NKG2D on tumor cells, and enhance NK cell mediated cytotoxicity [94]. Since tyrosine kinase inhibitors, histone deacetylase inhibitors and proteasome inhibitors affect the NK cell activity [103], Hsp90 inhibitors that show all the three effects [21,104] may probably help in the immunomodulatory functions of NK cells. The inhibition of Hsps using anti-Hsp90 inhibitors that can induce stress response and lead to induced synthesis of Hsp70 or over expression of Hsp70 have been suggested to elicit antitumor response. While Hsp90 inhibition was enhancing the lytic properties of tumor cells by the complement in a variety of tumor cells [77,101], Hsp70 over expression may activate the host antitumor activity, which may be comparable to that of in vivo effects [45,105,106].

Conclusions and Future Perspectives

We summarized potential involvement of Hsps in the innate tumor immunity and described how immune cells make use of Hsps in the immune cell signaling mechanism (Figure 2). We also provided comprehensive information on available and future chemotherapeutic strategies to alleviate innate immune signaling, and discussed how combination of anti-Hsp drugs augments the activation of immune signaling. There are many questions yet to be addressed, (1) whether inhibition of tumor cell signaling interferes with immune signaling, (2) whether chaperone inhibitors affect Hsp binding to tumor antigen and thus interferes with tumor based vaccine development, (3) whether Hsp co-recruiters or co-stimulators elicit unwanted or unwarranted stress response that instead of activating antitumor response promote tumor growth, (4) how the cross-talk between innate and adaptive immune signaling affected are by Hsp inhibition and (5) appropriate assessment of secondary effects of induced cell lysis by Hsp inhibition on host immunity.
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