



# Roles of heat shock proteins in tumor immune microenvironment

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**Abstract** – Heat shock proteins (HSPs) are the most abundant molecular chaperones in cells, categorized based on function and molecular weight into HSP families, namely, HSP40, HSP70, HSP90, HSP110, and HSPB (heat shock protein B), et al. HSPs are involved in protein homeostasis by assisting in the correct folding of proteins or incorrectly folded proteins, refolding partially denatured proteins, and degrading damaged proteins. High levels of HSPs have been shown to participate in oncogenesis, progression, and chemotherapy resistance in many cancers. Recently a new range of functions besides chaperons, mostly in modulation of immune responses, have been shown for these extracellular HSPs. Here, we review the interactions between the HSPs and different immune cells, such as T lymphocytes, B cells, dendritic cells, macrophages, NK cells, and myeloid suppressor cells in the tumor microenvironment, as well as tumor vasculature and angiogenesis in tumor formation. The underlying mechanisms of HSPs' regulation on immune response in tumor microenvironments are also discussed. The understanding of new functions of HSPs in tumor microenvironment may provide critical insights for the development of effective immunotherapies.

**Key words:** Heat shock proteins, Tumor microenvironment, Immune cells, Vasculature.

## Abbreviations

APCs:	Antigen-presenting cells	LOX-1:	Lectin-like oxidized low-density lipoprotein receptor 1
CRT:	Calreticulin	LRP1:	Low-density lipo-protein receptor related protein 1
CD4 <sup>+</sup> TIL:	CD4 <sup>+</sup> tumor infiltrating lymphocytes	LLC OVA:	Ovalbumin-transfected lewis lung cancer
DC:	Dendritic cells	MIP-2:	Macrophage inflammatory protein 2
eNOS:	Endothelial nitric oxide synthesis	MDSCs:	Myeloid-derived suppressor cells
ERK:	Extracellular signal-related kinase	MHC:	Major histocompatibility complex
FasL:	Factor related apoptosis ligand	MyD88:	Myeloid-differentiation factor 88
Foxp3:	Forkhead box p3	NKG2C:	Natural killer group 2 member C
GRP170:	Glucose regulated protein 170	NKG2D:	Natural killer group 2 member D
GRP78:	Glucose regulated protein 78	NKp30:	Natural killer receptor p30
GRP94:	Glucose-regulated protein 94	SR-A:	Class A scavenger receptor
HLA-DR:	Human leukocyte antigen DR	TAM:	Tumor associated macrophages
HSP:	Heat shock protein	Th1:	Type 1 CD4 <sup>+</sup> helper T cells
HSP90a:	Heat shock protein 90a	TKD:	Hsp 70 derived 14-mer peptide TKDNNLLGRFELSG
HSPA5:	Heat shock protein family A (HSP70) member 5	TLR-2:	Toll-like receptor 2
HSPB:	Heat shock protein B	TRAPs:	Tumor cell released autophagosomes
HSP-EX:	HSP-bearing exosomes	VEGFR-2:	Vascular endothelial growth factor receptor 2
HUVECs:	Human umbilical vein endothelial cells		
IDO:	Intracellular indoleamine 2,3-dioxygenase		
K5:	Kringle 5		

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Heat shock proteins (HSPs) are mainly induced by heat, radiation, infectious agents, heavy metal toxicity, and hypoxia. As molecular chaperones, HSPs are mainly categorized into several major families, including HSP40, HSP70, HSP90, HSP110, and HSPB (heat shock protein B), mainly distributed in the

intracellular, endoplasmic reticulum and mitochondria [1]. In addition to their chaperone functions, HSPs also play important roles in cell signaling transduction, cell cycle, and apoptosis regulation in many diseases [2]. Recently, the stress-induced HSPs were reported to serve as endogenous danger signal molecules to enhance the immunogenicity of tumors and induce the response of CTL cells [3]. Many HSPs receptors on the surface of antigen-presenting cells were discovered, including CD91 or LRP1 (LDL receptor-related protein 1), CD40, LOX-1 (Lectin-like oxidized low-density lipoprotein receptor 1), CD36, TLR-2 (toll-like receptor 2), TLR-4 (toll-like receptor 4) and SR-A (class A scavenger receptor) [4]. HSPs play a crucial role in regulating the immune response of tumors. Many studies have shown that HSPs could carry tumor-related antigens and be released in the form of extracellular vesicles, regulating the function of immune cells in the tumor immune microenvironment and thereby affecting tumor cell growth [5]. It was reported that inhibiting the expression of HSP90 in tumors significantly reduces T cell surface receptors CD3, CD4, CD8, CD28, CD40L, and CD25, while CD2, CD11a, CD94, NKp30, NKp44, and NKp46 on the surface of NK cells were significantly activated [6]. The heat shock proteins HSP90, HSP70, and antigen-peptide complex can be processed by antigen-presenting cells (APCs) such as macrophages and dendritic cells (DC), then represented by MHC class I molecules [7]. Herein, we focus on the roles of HSPs in the tumor immune microenvironment and delineate the cross-talk between HSPs and immune cells as well as vasculature.

## Heat shock proteins and T cells

HSPs bind to tumor antigen peptides to form a complex that is secreted and internalized by antigen-presenting cells such as macrophages and dendritic cells through endogenous pathways. They then bind to MHC-I molecules on the surface of antigen-presenting cells to activate CD8<sup>+</sup> T cells. Studies have found that compared to simple tumor antigen peptides, HSP-bound antigen peptides have a stronger ability to activate CD8<sup>+</sup> T cells through antigen-presenting [8, 9]. Endoplasmic reticulum chaperone glucose-regulated protein 170 (GRP170) is secreted by B16 melanoma as a danger signal molecule, inducing the secretion of IL-1 $\beta$  and TNF $\alpha$  by DC cells, simultaneously causing activation of antigen-specific CD8<sup>+</sup> T cells [10]. Introducing GRP170 into B16 melanoma cells induces anti-tumor immunity and suppresses distant lung metastasis of B16 melanoma [10]. Infiltrating CD8<sup>+</sup> T cells were increased and IFN- $\gamma$  and IL-12 accumulated around tumor cells [10]. Also, HSP70 purified from human melanoma cells activates CD8<sup>+</sup> T cells in an antigen- and HLA class I-dependent fashion [9]. GP96 (glucose-regulated protein 96) secreted from ovalbumin-transfected Lewis Lung Cancer (LLC OVA) cells activated DC cells, leading to a significant increase in cytotoxic CD8<sup>+</sup> T cell activity in mouse spleen cells. OVA-specific (+) CD8<sup>+</sup> T cells were mainly recruited near lymph nodes after activation [11].

CD4<sup>+</sup> T cells are divided into Th0 cells secreting IL-2, IL-4, and IFN-gamma, Th1 cells secreting IL-2 and IFN-gamma, and Th2 cells secreting IL-4 [12]. In the tumor microenvironment, the tumor antigen-HSP70 complex is recognized by the HLA

class II molecules on the APCs (antigen-presenting cells) surface. After antigen presentation, the tumor-specific CD4<sup>+</sup> TIL (CD4<sup>+</sup> tumor infiltrating lymphocytes) recognizes the HLA class I – or II on the surface of antigen presenting cells, resulting in a direct cytotoxic effect on tumor cells [12, 13]. Heat shock protein 90 $\alpha$  (HSP90 $\alpha$ ) expressed on the surface of tumor cell-released autophagosomes (TRAPs), then secreted from tumor cells to stimulate CD4<sup>+</sup> T cell by production of IL-6 via TLR2-MyD88-NF- $\kappa$ B signal cascade, thereby promoting tumor growth and metastasis [14]. BALB/c mice were immunized with exosomes containing HSP70 and type 1 CD4<sup>+</sup> helper T (Th1) cell responses were stimulated and a large amount of IL-2 and IFN- $\gamma$  were produced [15]. The immunogenic HSPs including GP96, HSP70, and calreticulin (CRT) can bind to CD91 on APCs for cross-presentation of the HSP-chaperoned peptides and lead to priming of T helper cells [16]. HSPA5 (heat shock protein family A (HSP70) member 5), also known as glucose-regulated protein 78 (GRP78), is an evolutionarily highly conserved protein. It is also an immunomodulator able to arrest inflammation through induction of tolerogenic DCs and subsequent generation of T regulatory cells. More HSPA5-treated DCs expressed amounts of intracellular indoleamine 2,3-dioxygenase (IDO) and produced copious amounts of IL-10. T cells co-cultured with HSPA5-treated DCs developed regulatory function with increased surface expression of CD4(+) CD25(hi) CD27(hi) but with no concomitant increase in Foxp3 (forkhead box P3) [17]. Taken together, HSPs can bind to tumor antigen peptide and stimulate antigen-presenting cells and finally induce T cell infiltration in the tumor microenvironment.

## Heat shock proteins and B cells

In addition to regulation of T cells, HSPA5 plays an important role in regulating B cells and other inflammatory processes. HSPA5 can induce IL-10-producing splenic B cells and B cells highly expressing PD-L1 and FasL. B cells treated with HSPA5 and anti-CD40 can lead to suppression of T cell proliferation [18]. GRP94 (glucose-regulated protein 94) is a tumor antigen shared by many types of solid and hematological tumors [19]. Stable complexes with IgG (GRP94-IgG) are detected in the plasma of patients with gastrointestinal tumors and served as diagnostic tumor marker [19]. HSP60 upregulates the expression of MHC class II in B cells and increase the expression of CD69, CD40, and B7-2 on the surface of B cells simultaneously [20]. After HSP60 treatment, B cells activate the cytotoxicity function of T cells and promote the secretion of IL-10 and IFN-gamma inflammatory factors [21]. Hence, HSPs can promote the expression of MHCII, PDL1, and CD69 on the surface of B cells, thereby activating cytotoxic T cells.

## Heat shock proteins and dendritic cells

DC cells are important antigen-presenting cells. They can bind tumor related antigens in extracellular vesicles or other special forms to DC cell surface related receptors in the tumor microenvironment. Through the opsonization of antibodies or

complements and a series of enzymes, tumor related antigens are presented to T cells in the form of antigen-peptide-MHC molecular complexes. Heat stress (high-temperature treatment) can induce the release of HSP70 from tumor cells, which, in turn, activate tumor cells to produce chemokines for chemoattraction of DC and T cells via TLR4 (toll like receptor 4) signaling pathway [22]. Exosomes derived from an engineered myeloma cells carrying membrane-bound HSP70 are able to more efficiently stimulate maturation of DCs with upregulation of Ia(b), CD40, CD80 and inflammatory cytokines than controls after overnight incubation of immature bone-marrow derived DCs [23]. In addition, exosomes carrying HSP70 and HSP90 derived from lung cancer cell line Rab27 upregulates MHC class II, CD80 and CD86 of DCs, leading to maturation of DCs and proliferation of CD4<sup>+</sup> T cells [24]. GP96 also mediates maturation of DCs as determined by upregulation of MHC class II and CD86 molecules [25]. Overall, HSPs are secreted from tumor cells and they can form complexes with tumor associated antigens in exosomes or other forms. For example, HSPs bind to DC cell surface receptors and upregulate related molecules such as CD80 and CD86, and finally activate T cell activity.

### Heat shock proteins and macrophages

Tumor associated macrophages (TAM) in the tumor microenvironment play a crucial role in tumor migration, invasion, angiogenesis, metastasis and drug resistance. Activated M2 macrophages can suppress normal immune cells and promote tumor development. Previous studies have shown that TAM can recognize vesicles secreted by tumor cells, leading to characteristics changes in TAM [26]. Studies have shown that eHSP-72 secreted from tumor cells can promote the secretion of more macrophage inflammatory protein 2 (MIP-2) by macrophages by interacting with TLR2 (toll like receptor 2) and TLR4 on the surface of macrophages [27]. Grp94, the most represented endoplasmic reticulum-residual HSP, is a specific antigen for solid tumors and hematological tumors that is recognized by immune cells after being transferred from the endoplasmic reticulum to the cell surface. Grp94-IgG complexes in the peripheral blood of tumor patients is significantly higher than that of healthy controls. Addition of Grp94-IgG complexes to macrophage culture medium revealed enhanced differentiation of macrophages in *in vivo* assay [19]. HSP70, secreted from tumor cells, binds to the membrane receptor CD14 of monocytes, inducing intracellular calcium ion flow formation and upregulating the pro-inflammatory cytokine IL-1 $\beta$ , IL-6 and TNF- $\alpha$  [28]. Macrophages were co-cultured with conditioned medium from HSP110 knock-down colorectal cancer cells HCT116 and SW480. Compared with controls, the macrophages expressed more HLA-DR receptors and secrete more TNF $\alpha$  and IL1b cytokines, while CD163 and CD206 were significantly reduced [29]. Similar results were observed in tumor samples of metastatic oral cancer. HSP90 $\beta$  secreted by tumors was recognized by TAM and promote TAM activation into M2 type [26]. In conclusion, HSPs, in the form of monomers, vesicles, or complexes, can affect macrophages' polarization, secretion of inflammatory factors and expression of surface receptors in the tumor microenvironment.

### Heat shock proteins and NK cells

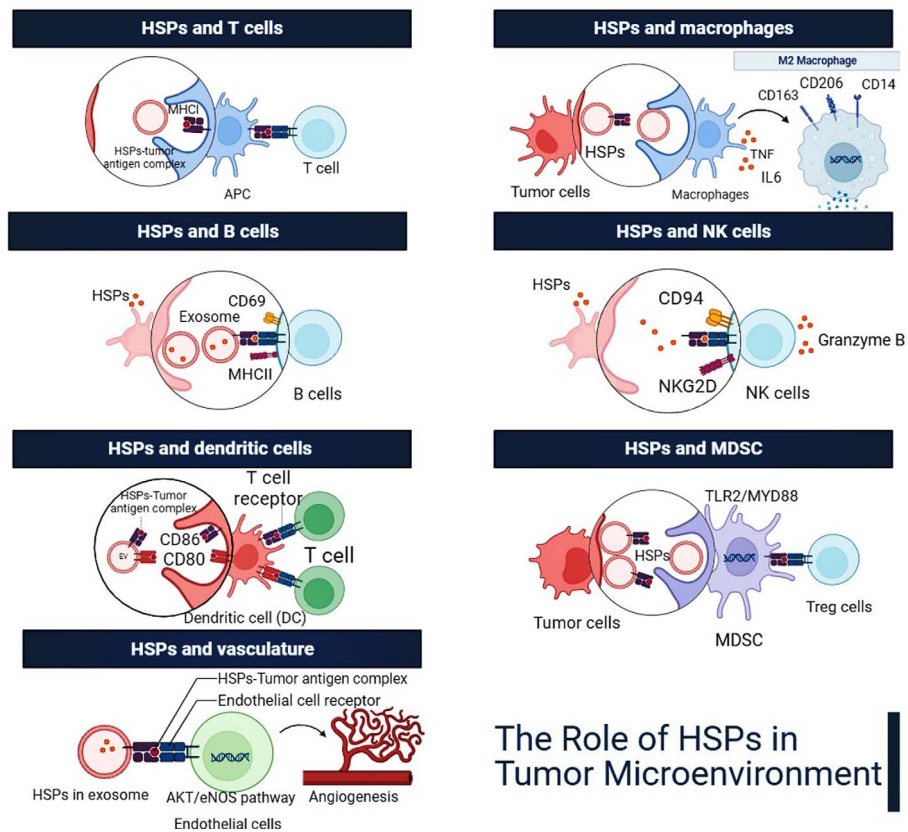
NK (natural killer) cells, as the first line of defense in the human body, release cytotoxic particles through the secretion of cytokines, leading to cytotoxic effects [30]. HSP70 peptide TKD (TKDNNLLGRFELSG, aa 450-463) is the N-terminal domain of HSP70. Studies have shown that the surface receptors of NK cells, CD94/NKG2C (natural killer group 2 member C), NKG2D (Natural Killer Group 2 Member D) as well as NKp30 (natural killer receptor p30), NKp44, NKp46, and NKp80 are upregulated under the influence of HSP70 derived TKD peptide [31–33]. However, HSP-bearing exosomes secreted from human hepatocellular carcinoma cells stimulate NK cells to secrete granzyme B into the tumor microenvironment [34]. Granzyme B, along with perforin, induces tumor cell apoptosis by forming transmembrane pores and cleavage of caspases [35]. HSPs efficiently stimulate NK cell cytotoxicity and granzyme B production, upregulate the expression of inhibitory receptor CD94 and downregulate the expression of activating receptors CD69, NKG2D, and NKp44 [36]. HSP70 can induce the release of granzyme B by inducing the opening of ion channels within NK cells [37]. HSP70 also activates mouse NK cells that recognize stress-inducible NKG2D ligands on tumor cells and results in a reduced tumor growth and suppression of tumor metastasis [38]. HSP70 peptide TKD was found to enhance the cytolytic activity of NK cells and NK cellsinitiated apoptosis in tumors through granzyme B release [39, 40]. Taken together, HSPs can induce cytotoxicity of NK cells by affecting surface receptors such as NKp44 and NKp46, as well as the secretion of granzyme B, thereby inhibiting tumor growth.

### Heat shock proteins and MDSCs

MDSCs (myeloid-derived suppressor cells) are precursors of DCs, macrophages, and granulocytes. MDSCs are heterogeneous populations of cells that expand during cancer, inflammation and infection [41]. MDSCs are divided into two major groups: granulocyte MDSCs (CD11b+Ly6C-Ly6G+) and monocyte MDSCs (CD11b+Ly6C+Ly6G-) [42]. MDSCs can recognize HSP72- or HSP70-bearing exosomes and be activated via TLR2/MyD88 pathway or NF- $\kappa$ B pathway [5]. Activated MDSCs enhances Treg activity and TGF- $\beta$  secretion [5]. Therefore, MDSC can recognize HSPs and signaling pathways within MDSC are activated, which in turn promote the activity of Treg cells.

### Heat shock proteins and vasculature

The tumor vasculature is essential for tumor growth and survival and is a key target for anti-cancer therapy. The basic process of tumor angiogenesis is mainly caused by activation of endothelial cells under growth factor stimulation, basement membrane degradation, and recruitment of pericytes to stabilize the newly formed capillary network [43]. HSPA5 is generally highly elevated in the vasculature derived from human glioma specimens and targeting HSPA5 can sensitize the tumor vasculature to chemotherapeutic drugs, such as CPT-11, etoposide

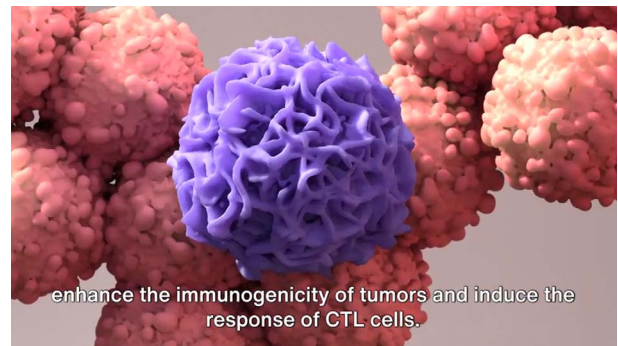


## The Role of HSPs in Tumor Microenvironment

**Figure 1.** The interactions between HSPs and different immune cells and tumor vasculature in tumor microenvironment.

and temozolomide [44]. HSPA5, exposed on cell surfaces of proliferating endothelial cells as well as on stressed tumor cells, plays a key role in the antiangiogenic and antitumor activity of human plasminogen Kringle 5 (K5) [45]. HSP70-1 is also an angiogenic regulator. It is tightly bound to the surface of HUVECs (human umbilical vein endothelial cell) and participates in extracellular signal-related kinase (ERK)-dependent angiogenesis [46]. IL-5 as an activator of angiogenesis, promotes ERK and AKT/endothelial nitric oxide synthesis (eNOS) phosphorylation in HUVECs cells, as well as promotes microvessel sprouting from an angiogenic animal model [47]. Binding of IL-5 to IL-5R $\alpha$  receptors enhances angiogenic responses by stimulating the expression of HSP70-1 via the eNOS signaling pathway [48]. In addition, HSP90 inhibitors exert anti-angiogenesis effects by affecting the PI-3K/Akt/eNOS signal transduction pathway within endothelial cells and reducing the expression of VEGFR-2 on the surface of endothelial cells. In addition, blocking the expression of HSP90 can reduce the expression and secretion of pre-angiogenic proteins derived from tumor cells, which indirectly induces the anti-angiogenic effect of tumors [48]. In summary, HSPs can bind to receptors on the surface of endothelial cells, activate the eNOS signaling pathway and promote angiogenesis in the tumor microenvironment.

Recently, HSPs have been reported to be secreted through exosomes by tumor cells. HSP-exosomes have been reported as biomarkers of cancer dissemination, response to therapy or



**Video 1.** Roles of heat shock proteins in tumor immune microenvironment. This video was generated by using a commercially available artificial intelligent platform Invideo AI. <https://vcmedpsciences.org/10.1051/vcm/2024002#V1>.

patient prognosis [49]. A new range of functions, mostly in modulation of immune responses, have been shown for these extracellular HSPs. The understanding of the pivotal role of HSPs in tumor microenvironment and the underlying regulatory mechanisms will increase our knowledge of the etiology of cancer, as well as development of immune therapy against cancer. However, vaccines targeting HSPs are not very clinically successful, and more research is needed. This review explores interactions between HSPs and different immune cells as well

as tumor vasculature in tumor microenvironment (Figure 1, Video 1). HSPs might be both targets for anticancer therapeutics and biomarkers for the monitoring of cancers. It is also an emerging target for cancer vaccines.

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### Conflict of interest

The authors declare no conflict of interests.

### Data availability statement

The data are available upon request.

### Author contribution statement

QZ wrote the initial draft; XYG provided funding support; YL provided funding support, supervised the study and wrote the final manuscript. All authors have read and agreed the manuscript.

### Ethics approval

This is a review and it does not need ethics approval.

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