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Cell Surface Heart Shock Proteins and their Role in Cancer

Gopal A[1] and Gopal U[2*]

[1]Department of Biotechnology, Center for Biotechnology, Anna University, India

[2]Department of Pathology, Duke University Medical Center, USA

Review Article

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***Corresponding author:** Udhayakumar Gopal, Department of Pathology, Duke University Medical Center, Durham, NC, USA, Tel: 91-684-8986, Fax 91-684-8689; E-mail: udhayakumar.gopal@duke.edu

Abstract

Heat-shock proteins are commonly considered to be an intracellular molecular chaperone which performs multitude of functions like cytoprotective and cellular housekeeping functions. However many of these chaperones translocate into the surface of the cells particularly during stress induced conditions like hypoxia, UV-radiation, chemotherapy, drugs and microbial stimuli. Once on the cell surface or in the extracellular space, the heat shock proteins functions like receptors for wide variety of ligands by which it regulates signaling, proliferation, invasion, apoptosis, inflammation and immunity. Thus, cell-surface Heat-shock proteins may play a unique role in tumor metastasis, distinct from but perhaps overlapping with its intracellular function. The discovery of cell surface Heat shock proteins in cancer cells and cells undergoing stress presents a novel therapeutic strategy.

Keywords: Heat shock Protein; Cell surface; Cancer; ER Stress; CS-HSP90; CS-GRP78

Introduction

Molecular Chaperones are proteins that permit the maturation and correct folding of most of the proteome [1,2]. As such, they are found in all cellular organisms and seem essential for cellular life. Protein folding seems to require chaperones from a number of different gene families that appear to function at various stages in a concerted folding cascade. These proteins belong to the small heat-shock protein (HSP) family including HSP27 and the large 70Kda HSP family including HSP70 as well as HSP60, HSP90, and HSP110 families [3]. The acronym HSP is derived from the early findings that some of these proteins are massively induced during proteotoxic stresses such as heat shock [4]. Thus the canonical functions of the HSP chaperones are in the folding of proteins during mRNA translation and in responding to protein unfolding crises in stressed cells [5].

Cell-Surface HSPs and Cancer Metastasis

However, HSPs also appear to possess functions outside the realm of protein folding, some of them acquired when they are released from cells to become Cell Surface (CS)-HSPs [5-8]. HSPs have been observed in serum from human patients, pointing to their existence outside of cells in living organisms [9]. The properties of extracellular HSPs have now expanded from immune response to major intercellular signaling molecules in biology and medicine. In this review we describe only the functions of CS-HSPs in cancer and their possible role in various pathologies.

As summarized in (Table 1) it has been shown that HSP are expressed on the cell surface and that these proteins are crucial for cancer progression. HSP25 a murine homolog of human HSP27, has been shown to regulate metastasis [10]. Surface expression of HSP25 correlates

with enhanced breast cancer growth in vivo and cells expressing higher levels of HSP25 on the cell surface display enhanced metastatic potential in vitro and enhanced metastatic activity in vivo. HSP70, a major stress- inducible chaperone is expressed at the cell surface of melanoma metastases but not in normal skin fibroblasts [11]. Cell surface expression of HSP70 is observed to be significantly higher in clinically advanced oral tumors [12], suggesting that cell surface HSP70 might be crucial for tumor progression. In contrast, CS-HSP70 seems to inhibit metastasis in breast cancer cells [10]. This discrepancy may be due to the difference in cell type.HSP90 identified on the cell-surface is crucial for cell motility in neuronal, glioma and melanoma cells [7-34]. CS-HSP90 interacts with low-density lipoprotein receptor-related protein (LRP1/CD91) to induce a number of pro-motility signaling cascades that are essential for wound healing [15]. In glioma cells extracellular HSP90 promotes interaction of LRP1 with ephrin type-A receptor tyrosine kinase 2 (EPHA2) by activating AKT signaling which induces pro-motility function [7].

ER HSPs	Over expression in diseases	Potential role	Reference
HSP47	Oral Cancer	Migration and Invasion	[25]
GRP78	Prostate, Glioblastoma	Tumor proliferation, gene activation	[26,27]
ERP57	Breast and Gastric cancer	Tumor proliferation	[28,29]
PDI	Prostate and Lung Cancer	Migration	[30,31]
GP96	Ovarian and Pancreatic cancer	Immune response	[32]
Calreticulin	Melanoma	Migration	[34]

Table 1: Summary of CS-HSPs in Cancer.

Endoplasmic Reticulum (ER) Chaperones

The Endoplasmic reticulum (ER) is one of many specialized organelles in the cell with diverse and apparently ever expanding functionality. Two of the major functions of the ER, namely calcium sequestration [16] and the correct assembly, folding and secretion of glycoproteins were established over the decades [17-19]. In ER number of proteins functions like heat shock proteins which are HSP47, GRP78, ERP57, protein disulfide isomerase (PDI), gp96 and calreticulin [20]. During chemical or physical cell stress chaperones relocate to the cell surface where it's associated with various diseases particularly cancer (Table 2). Over expression of chaperones on the cell surface to cope with increased ER stress due to malignancy. CS-ER chaperones might be simply a biomarker and we highlight their direct role in the spread of tumors by promoting cell proliferation [21], migration [22] and metastasis [23,24].

HSPs	Over expression in diseases	Potential role	Reference
HSP25	Breast Cancer	Increases metastasis	[10]
HSP70	Oral Tumor, Melanoma	Tumor proliferation, Metastasis	[11,12]
HSP90	Glioblastoma, Fibroblast	Migration, Wound healing	[7,15]

Table 2: Summary of CS-ER HSPs in Cancer.

Cell Surface ER Chaperones and Cancer

HSP47, which is known as a rheumatoid arthritis-related antigen, has been shown to be expressed at the cell surface, and oral cancer cells expressing high levels of surface HSP47 display low invasive activity, suggesting that HSP47 has an inhibitory effect on cell migration/invasion [25]. Thus, may distinct chaperone proteins might be expressed at the cell surface, and have diverse effects on cell motility, invasion, and cancer progression.GRP78 expresses on the cell surface where it functions as a multifunctional receptor for a wide variety of ligands to mediate proliferative signaling in various human cancers. Though the GRP78 forms complexes with other proteins on the cell surface, GRP78 is reported to mediate tumor cell signal transduction. Cell Surface GRP78 is also an angiogenic receptor on endothelial cells by increasing its proliferation, migration and tube formation [26]. Moreover, CS-GRP78 is required for the transcriptional activation of a subset of c-Myc target genes and cell transformation [27]. It suggests that CS-GRP78 function not only as a signaling mediator but also activates transcription factors in tumor growth.

ERP57 increases in the cell surface regulate EGF receptor signaling and internalization in breast cancer

cells. Moreover secretion of ERP57 is essential for matrix accumulation and prognostic significance in gastric cancer [28,29]. CS-PDI is upregulated in CNS cancers, lymphoma's ovarian, lung and prostate cancer. Furthermore it regulates multiple important biological processes like injury response and it promotes glioma cell migration [30,31]. GP96, the HSP90 homology in endoplasmic reticulum, has been shown to be expressed at the cell surface only in tumor cells [32], and it was the first chaperone described to play a role in the induction of anti-tumor immune responses. Several phase I and phase II clinical trials are currently ongoing using a GP96-peptide complex as a cancer vaccine. The role of GP96 in mediating immune responses was well summarized in a recent review [33]. Calreticulin, an endoplasmic reticulum chaperone is also expressed at the cell surface. Calreticulin has been identified as the cell surface lectin responsible for triggering cell spreading of melanoma cells [34]. Treatment of cells with calreticulin antibody inhibited laminin-dependent cell spreading, suggesting that calreticulin is crucial for cell motility and that it might participate in integrin signaling. Indeed, it is reported that calreticulin is associated with integrin α-2/β-1 on the platelet surface and that it modulates ligand interaction with integrin's [35].

Conclusion

Chaperone molecules play a number of specific roles related to protein processing within the cell. It's also well known that HSPs play a central role in cancer development and progression. However, new knowledge indicates that a select number of chaperones in the extracellular environment can play a role in tumor growth as well as invasion and metastasis. Therefore it is crucial to understand how various post-translational modified forms of chaperones are release from cells under resting and stressed conditions and how the released chaperones exerts their proliferative and cell survival responses. The precise nature of the functions and molecular mechanisms of CS-HSPs is crucial for enhancing the accuracy of cancer diagnosis as well as for developing more effective therapeutic agents.

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