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Identifying Molecular Chaperones as Therapeutic Targets for Cancer: A Mini Review

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Abstract

Cancer is the name given to a complex set of diseases that follow a common pathway of progression i.e., localized proliferation, invasion and metastases. The disease is common world over and the number of affected people (14.9 million in 2013) is projected to increase further in coming decades. The treatment regimen at present is a combination of surgery, chemotherapy and/or radiation. Significant numbers of patients exhibit resistance to these modalities and experience relapses. The cost of treatment, emotional burden and effect on standard quality of life due to cancer is huge. Research over last few decades has broadened our understanding of cancer. At the molecular level detailed studies of many cancers have resulted in characterization of proteins for efficient and targeted therapeutic drug design. Molecular chaperones are such groups that have been targeted over last few decades for development of anticancer compounds. This review is aimed at compiling the information relevant to this field.

Keywords: Chaperones; Heat shock proteins; Peptidomimetic drugs; Epithelial-mesenchymal transition

Cancer–Need of Drug Design

According to combined NCI, ACS and CDC report for 2016, in US alone, 1.7 million new cancer cases and 0.6 million fatalities due to cancer have been projected [1]. Over past fifty years tremendous progress has been made in treatment regimen challenging the concept of cancer being incurable. Due to the advances in chemo and radiation therapy, diagnosis of cancer is not always thought of as a death sentence. The 5-year survival rate has shown an upward trend during this time (standing at 19% in 2012). But cancer has proven complex, increasingly resistant and highly prone to relapse. For the sake of comparison, unlike AIDS, cancer doesn't have a singular viral origin and unlike Alzheimer's or Parkinson's it is not restricted to biochemical manipulation through one protein in one organ only. By no means do we want to infer that other diseases are any less complex but cancer is quite heterogeneous at the molecular and cellular levels. Further, diversity in terms of causes, types, organs affected, severity, and metastases has made it very difficult to combat this disease (system) [2]. Therefore, an immediate need of drug development is imperative that in turn requires extensive elucidation of the intricate mechanisms of cancer progression. The unraveled targets thus could be used for efficient anti-cancer drug design.

Proteins (Chaperones) as cancer targets

The use of proteins as anti-cancer targets started in the late 1940s when aminopterin were used to block folate-requiring enzymes for treating children suffering from acute lymphoblastic leukemia [3,4]. Since then quite a few protein kinases and signal transducing protein molecules have been targeted for anticancer drug design, especially, the well documented and successful bcr-abl kinase in the case of chronic myelogenous leukemia (CML). The initial drug molecule 'imatinib' exhibited stellar success in CML reducing relapse to 0.6% [5] and its modified derivatives (e.g., AP24532) inhibited the most resistant mutants (T315I) in relapsed CML cases [6]. Her2 and others provide further successful cases of protein based anti-cancer drug design. These examples therefore provide inspiration for discovery of new protein targets and subsequent drug design against them for cancer cure. Chaperones are important cellular proteins that have also been actively targeted for anti-cancer therapeutic development over last two decades [7].

Molecular chaperones

Chaperones are a group of proteins that exhibit protective nature towards other proteins [8]. Chaperones were identified through a heat shock on Drosophila [9] and are also referred to as "Hsp's". Members of the chaperone family are differentiated on the basis of their molecular weight (Table 1) [3]. Under physiological conditions chaperones fold nascent polypeptide chains or unfolded proteins into their active conformation [10,11] at the expense of ATP consumption.

Additional proteins termed "co-chaperones" support each family in a meticulous, concerted and regulated manner [12]. Some co-chaperones and chaperones lack ATP activity and are unable to fold protein but can still prevent unwanted aggregation or toxicity through binding to client proteins thus behaving as 'holdases' [13].

Involvement of chaperones in cancer was supported by evidence that levels of chaperone transcription factor (HSF1) are directly related to the severity of cancer [14-16]. Thus molecular chaperones were targeted as anti-cancer drugs since early 1990s [17]. We will discuss anti-cancer drugs designed on some "Hsp's" below.

Chaperone (new nomenclature)	Mol. Wt. (kDa)
HSPA	70
HSPB	<30
HSPC	90
HSPD	60
HSPE	10
HSPH	>100
DNAJA, B, C	40

Table 1: A partial list of chaperones [3].

Small Heat Shock Proteins (sHsps)

sHsps are low molecular weight (12–43 kDa) proteins with a conserved crystalline domain near their C-terminus and this family comprises of 11 known members [18]. Hsp27 (HSPB1) and αB-crystallin (HSPB5) are the most studied sHsps. In mammalian cells, sHsps oligomerize forming 50–800 kDa units that can be homo- or hetero-meric in composition, acting as reservoirs and have been proposed to dissociate under stress conditions in order to prevent aggregation of proteins [19]. The chaperoning activity of sHsps is ATP independent, however, phosphorylation leading to their dissociation could be important for their chaperoning activity [20]. The unfolded proteins sequestered by sHsps can be either transferred to Hsp70 for re-folding [21] or passed to the proteasome for degradation [22].

sHsps have been implicated in most of the common cancers including breast, ovary, colon, prostate, lung and brain [23-28]. sHsp levels in these cancer have been observed to be at higher level than normal. For breast cancer sHsps have been found to increase Her-2 stability [29]. PTEN, an important tumor suppressor, appears to be downregulated by HspB1 [30]. Small Hsps appear to influence the important markers of cancer [2] as we mention here. HspB5 through MEK/ERK pathway induces anchorage independent growth in basal-like breast carcinomas [23]. Oncogene-induced senescence (OIS) is an important defensive anti-cancer response. OIS involves, p53, p21, HDM2 and P13/AKT pathways. HspB1 expression in primary colorectal cancers has been shown to overcome PI3K/AKT induced OIS [31]. Epithelial-mesenchymal transition (EMT) is regarded as the first step in cancer metastases and metastatic tumors at their original and new sites replenish themselves by angiogenesis. In breast cancer, HspB1 has been proposed to augment EMT and its silencing led to elimination of EMT [32,33]. HspB1 enhanced EMT through cell migration, invasion, MMP-2 activity and N-cadherin [34]. HspB5 binding leads to stability of endothelial growth factor (VEGF-A) thus facilitating angiogenesis [35]. HspB1 has also been implicated in rare cancers involving loss of heterozygosity (LOH). A higher HspB1 expression correlated with LOH of 1p associated with oligodendroglial tumors [36]. Phosphorylation is an important posttranslational regulator of sHsp activity. For example, serine 59 phosphorylation reduces the oligomerization and anti-apopototic activities of HspB5 [37]. Phosphorylation of HspB1 can either increase [38] or decrease sensitivity of cancers toward therapeutics [39].

Based on these studies, sHsps have been proposed to be efficient targets for anti-cancer drug development. Since these chaperones are active in the oligomeric state, combining mutant subunits inhibits the contribution of sHsps in proliferation [40]. Peptidomimetic drugs like the peptide fragment (EFQFLDI) from protein kinase C has been shown to inhibit HspB1 mediated resistance to chemotherapy [41,42]. Small interference RNAi such as OGX 437 against HspB1 has been reported to decrease aggressiveness of tumors [43]. Some anticancer drugs with high specificity for sHsps have also been reported for example KRIBB3 [44], brivudine [45], diterpenoids [46]. It is discouraging to find that some anticancer drugs like cisplatin, vincristine and colchicine enhance HspB1 or HspB5 expressions [47].

Hsp70

Hsp70 is constitutively expressed in most species. For example, out of all sequenced bacteria (over 1200 genomes), only two members of the order Aquificales do not possess HSP70 genes [48].

Hsp70 is the main workhorse of folding machinery in humans that helps nascent or unfolded proteins to fold into biologically relevant structure. In Hsp70 folding cycle a client protein, either itself or facilitated by Hsp40, first binds to Hsp70 C-terminal substrate binding domain (SBD) with ATP bound in its N-terminal Nucleotide binding domain (NBD). A substrate/Hsp70/Hsp40 ternary complex formation is thus formed [12]. Nucleotide exchange factors (NEF) replace ATP dissociating the complex with concomitant release of the folded substrate [49]. If the substrate fails to fold it enters Hsp70 cycle repeatedly until it is successful otherwise it gets tagged for degradation through the CHIP-ubiquitin pathway. The system also participates in apoptosis [50]. While Hsp70 and its co-chaperones are believed to act in a concerted fashion we have shown the individual members can have differing effects on the substrate molecule [51]. Hsp70 cycle under duress has been shown to help healthy folding of oncogenic proteome facilitating tumorigenesis (Figure 1) [52].

The strongest indication of Hsp70 involvement in cancer comes from its overexpression in tumors [53-55]. In addition, Hsp70 suppresses tumor through senescence pathways [56]. Downregulation of Hsp70, Hsp70.2 and mitochondrial Hsp70 induces apoptosis in breast cancer cells [57]. Upregulation of Hsp70 causes resistance to cell death in pancreatic cancer [58]. Metastatic hepatocellular carcinoma cell lines have been reported to exhibit higher levels of mortalin (mitochondrial Hsp70) and mortalin-mRNA [59].

In our recently published articles we showed through NMR studies the development of two drug like molecules: i) Telmisartin that disrupts Hsp70/GrpE interaction, and ii) Zafirlukast that disrupts Hsp70/Hsp40 interaction [60]. In another recent article again our NMR studies showed development of a modified form of MKT-007, an anti-cancer drug that was 3-fold more active than original MKT-007 on breast cancer cell lines MDA-MB-231 and MCF-7 with biological half-life in microsomes improved 7-fold over the original compound [61]. Thus, these initial findings clearly indicate there is potential for anti-cancer drug development targeting the Hsp70 system and systematic investigations in this direction could be highly applicable in finding cancer cure.

Hsp90

Hsp90 is a dimeric protein with each monomer consisting of a Nucleotide-Binding Domain (NTD), a substrate binding domain also known as Middle Domain (MD) and a c-Terminal Domain (CTD). In a typical Hsp90 cycle the substrate (unfolded protein) either free or handed over by Hsp70 system binds to MD while NTD is in ATP state

[62]. Co-chaperones such as p23, Sba1, Cdc37, p50 or other similar proteins subsequently bind and stabilize the complex allowing substrate to regain its folding. ATP hydrolysis triggered by proteins like Aha1 then disintegrates the complex leading to the release of the folded substrate. Hsp90 dimer stays connected by CTD and starts a new cycle by acquiring fresh ATP. Hsp90 is highly promiscuous molecule and its folding cycle involves contribution of many other co-chaperones that simply cannot be discussed here [63].

Involvement of Hsp90 in cancer is indicated by inhibition of Hsp90 causing accumulation of misfolded oncogenic proteins [64]. Hsp90 thus was one of the first chaperone targets used for anti-cancer drug design [17]. To this extent, Hsp90 has recently been named an unlikely ally in the war on cancer [65,66]. Its co-chaperones are equally deemed as targets. We mention here P23 that is among many of Hsp90 co-chaperone. P23 is overexpressed in breast cancer [67], is involved in prostate cancer through androgen receptor activity [68] and is overexpressed in acute lymphoblastic leukemia where it inhibits chemotherapy-induced apoptosis [69].

The first inhibitors of Hsp90 were geldanamycin and radicicol that exhibited anti-cancer properties [7,17]. Their modified and more active forms are being designed routinely. More soluble and less toxic compounds like 17-AAG, KOS-953, have shown promise in cancer treatment [70]. Other drug like celastrol interferes with Hsp90/Cdc37 complex inhibiting growth-regulating pathway and is considered a promising candidate for prostate cancer treatment [71]. Drug 'gedunin' binds to P23 and restores the apoptotic pathways of malignant cells [72]. Some drugs like retaspimycin (IPI-504), ganetespib (STA9090) are ongoing phase 1-3 clinical trials targeting Hsp 90 in various cancers [73].

Hsp110

Three or four related HSP110 (HSPHs) genes are predicted to be expressed in all the ATP containing compartments of the cell: cytosol, nucleus, lumen of the Endoplasmic Reticulum (ER), mitochondrial matrix and in plants, the chloroplast stroma and the glyoxisome [74,75]. Hsp110 appears to exist in two isoforms the constitutively expressed cytosolic Hsp105α and stress induced nuclear hsp105β [76]. Hsp110 crystal structure was solved by Hendrickson group in 2007 [77] and was observed to share striking similarity with Hsp70. Like Hsp70, Hsp110 was found to consist of ATP binding NBD domain and substrate binding SBD domain connected by a linker. Further, the NDB of Hsp70 and Hsp110 exhibited 35% sequence identity and the SBDs of two molecules shared 15% identity. Unlike Hsp70, Hsp110 does not undergo a folding cycle but instead acts as a NEF for Hsp70 system besides serving as "holdase" [78].

Hsp110 was reported to be one of the most highly upregulated proteins in a variety of human cancers [79]. Hsp110 has been implicated in cancer through manipulation of proteins or RNA [80]. Depletion of Hsp110 in B-cell non-Hodgkin's lymphoma led to downregulation of BCL6 and c-Myc oncogenes [81] and was observed to promote macrophage polarization towards a cytotoxic phenotype [82]. Similarly, levels of Hsp110 correlate with the progression of colon cancer [83].

Further, Hsp110 was observed to increase resistance to chemotherapy and promote cell proliferation by phosphorylating STAT3 [84]. Hsp110 has been observed to participate in Wnt-mediated proliferation. Knockdown of Hsp110 results in degradation of β-catenin and inhibition of proliferation in colon cancer cell lines [85]. Since most colon cancers involve active Wnt/β-catenin signaling, Hsp110 could also be used as a biomarker [86].

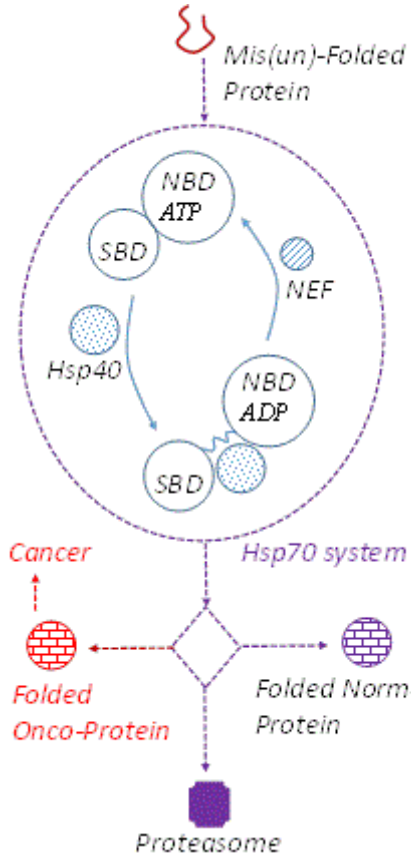

Figure 1: Summary of Hsp70 cycle and its contribution in cancer.

Based on its involvement in cancer, Hsp110 has been used as a vaccine to trigger immunogenic response for anticancer effects. Vaccination with Hsp110–ICD (Her-2 intracellular domain) complex inhibited development of breast tumors in transgenic mice [87]. On similar lines Hsp110-gp100 complex was found to have efficacy against B16 melanoma [88]. In addition, mice immunized with irradiated colon cancer cells (Hsp110-CT26 cells) inhibited the growth of unchanged CT26 tumor and resulted in increased tumor-specific T cells [89]. Hsp110 has also been targeted in other ways. Synthetic RNAi against Hsp105 was able to induce apoptosis in different cancer cells lines [90]. KnK437, a pan Hsp inhibitor was reported to acts on Hsp105 too and sensitizes colon carcinoma cells [91].

Conclusion

Besides above mentioned, there is a repertoire of chaperones that have been targeted for anticancer drug design [92,93]. Therefore, chaperones at the molecular level appear to cross the pathway of cancer progression at many levels and in many forms and some of their inhibitors have advanced in clinical trials. In light of these convincing data, it is reasonable to pursue rational drug design using chaperones as anticancer therapeutic targets.

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