Molecular Chaperones and Co-chaperones as Therapeutic Targets for Cancer

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Introduction

Cancer is a devastating disease that has affected millions of people, consumed tremendous efforts in the treatment/care and is incurable. Statistics from www.seer.cancer.gov show 14,140,254 people were living with cancer in 2013 in US with 1,685,210 new cases projected and 595,690 estimated deaths to occur due to cancer in 2016. Number of people surviving cancer (measured as 5-year survival rate) has increased by 18% (48.7% in 1975 to 66.9% in 2012) during the last half century. This number appears to be small if we consider the contribution of proactive care for example, early detections, and attention to lifestyle and aggressive chemical/radiation therapy and at the same time stare at a bleak hope of any apparent breakthrough in next 10 years. On the other hand, gain of even a small percentage in the survival of cancer can be regarded significant considering its complexity in terms of causes, types, organs affected, severity, origins and metastasis each of which has made it very difficult to combat this disease (system) [1]. For the sake of comparison, unlike AIDS, cancer is not limited to a pathogen and immune system only and unlike Alzheimer's or Parkinson's it is not restricted to one protein and one organ only. This is not to say other diseases are less complex but certainly not as diverse as cancer. Hence, knowing well the challenges in dealing with an intricate system and to develop a cure, the need for extensive investigation in the area of cancer is imperative.

Drug Design for Cancer

Keeping the transcriptome (RNA) influence aside because of its infancy in the field, we can generalize that: oncogenic stimuli by an extrinsic carcinogen or intrinsic oncogene (proto oncogene/genetic manipulation) gets transcribed in genome and manifests itself through proteome. Literature is filled with examples of protein kinases and signal transducing protein molecules, under oncogenic conditions, playing a pivotal role in the transformation of normal tissue leading to poor prognosis. And precisely for this reason, proteins have been used as targets for drug design against cancer and sometimes with good success. One such textbook example is provided by drug design against bcr-abl kinase that causes chronic myelogenous Leukemia (CML). Tireless efforts by dedicated scientists resulted in the design of a molecule ‘imatinib’ that inhibited bcr-abl kinase reducing the annual refractive to imatinib inhibition. But diligent investigations led to the complexity in terms of causes, types, organs affected, severity, origins and metastasis each of which has made it very difficult to combat this disease (system) [1].

Molecular Chaperones

Chaperones were identified around 1962 as proteins produced by heat shock in Drosophila [5] and soon a big family of these molecules was discovered. They were thus called Heat Shock Proteins (HSP) and differentiated on the basis of their molecular weight. For example, HSP60 is a 60 kDa chaperone molecule. The name “chaperone” was proposed by Ellis based on the protective nature of these proteins [6]. For simplicity, recent classification has grouped HSP molecules into different families viz., Hsp90 (HSPC), Hsp70 (HSPA), Hsp60 (HSPD), small Hsp (HSPB) and large Hsp (HSPH) [7]. Normal function of chaperones is to fold nascent polypeptide chains or unfolded proteins into their active conformation, [8,9]. They achieve this at the expense of ATP hydrolysis. Each family is further composed of additional members that help in carrying out concerted steps meticulously [10]. These supporting proteins are called “co-chaperones.” Co-chaperones and many chaperones lack the ability to hydrolyze ATP and are unable to fold protein on their own but at the same time they may bind to client proteins and prevent unwanted aggregation or toxicity. In such cases they are referred to as ‘holdases’ [11].

Molecular chaperones were identified as anti-cancer drugs since early 1990s [12]. We will discuss anticancer drugs designed using Hsp90 and Hsp70 as examples.

Hsp90

Hsp90 is a dimeric protein with each monomer consisting of three domains; i) top nucleotide binding domain ([NTD) binds ATP], ii) middle domain ([MD) binds substrate protein] and iii) bottom c-terminal domain ([CTD) responsible for dimerization]. Hsp90 is highly interactive protein exhibiting a huge list of protein partners (https://www.picard.ch/Hsp90Int/index.php) that makes it difficult to provide a concise mechanism. A typical Hsp90 cycle however involves binding of the substrate (unfolded protein) either free or handed over by Hsp70 system mainly to MD while NTD is in ATP state [13]. Subsequent binding by co-chaperones like p23, Sba1, Cdc37, p50 or similar others stabilize the complex either by inhibiting ATP hydrolysis or enhancing 90-substrate interactions. This allows substrate a chance to regain physiological folding. Proteins like Aha1 then trigger ATP hydrolysis and disintegration of complex leads to release of folded
substrate. Hsp90 dimer still connected by CTD is ready to take new ATP and undergo a fresh cycle. The folding cycle involves contribution of many other co-chaperones that simply cannot be discussed here [14].

Inhibition of Hsp90 causes accumulation of misfolded oncogenic proteins [15]. Hsp90 thus was one of the first chaperone targets used for anti-cancer drug design [12]. Since then it has progressed further and Hsp90 has recently been named an unlikely ally in the war on cancer [16,17]. Its co-chaperones are equally deemed as targets. P23 is among many of Hsp90 co-chaperone that is overexpressed in breast cancer [18], is involved in prostate cancer through androgen receptor activity [19] and is overexpressed in acute lymphoblastic leukemia where it inhibits chemotheraphy-induced apoptosis [20].

Since the first Hsp90 inhibitors geldanamycin and radicicol exhibited anti-cancer property development of more drugs in this direction have been designed [4,12]. More soluble and less toxic compounds like 17-AAG, KOS-953, have shown promise in cancer treatment [21]. Celastrol interferes with Hsp90/Cdc37 complex inhibiting growth-regulating pathway and is considered a promising candidate for prostate cancer treatment [22]. Drug ‘gedunin’ binds to P23 and restores the apoptotic pathways of malignant cells [23]. Drugs like Retaspimycin (IPI-504), Ganetespib (STA-9090) are candidates in the prostate cancer treatment [22]. Drug ‘gedunin’ binds to P23 and also participates in apoptosis [26]. While Hsp70 and its co-chaperones [32-34]. In addition, Hsp70 suppresses tumor through senescence pathways [35]. Hsp70, Hsp70.2 and mitochondrial Hsp70 when overexpression in tumors [29-31]. Sometimes levels of chaperone have been reported to exhibit higher levels of Mortalin (mitochondrial Hsp70) and Mortalin-mRNA [38].

Our NMR work in recently published article showed development of two drug like molecules i) Telmisartan that disrupts Hsp70/GrpE interaction and Zafirlukast that disrupts Hsp70/Hsp40 interaction [39]. 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 [40]. Thus, these initial findings clearly indicate there is potential for anti-cancer drug development targeting Hsp70 system and systematic investigations in this direction could by highly applicable in finding cancer cure. Further, other chaperones besides Hsp70 and 90 have also been targeted for drug design [41,42].

In conclusion, chaperones appear to cross the pathway of a transforming cell at many levels and in many forms and some of their inhibitors have advanced in clinically trials. These facts are convincing reasons to pursue rational drug design using chaperones as anticancer therapeutic targets.

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References

1. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144: 646-674.
2. Drucker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, et al. (1996) Effects of a selective inhibitor of the Abi tyrosine kinase on the growth of Bcr-Abi positive cells. Nat Med 2: 561-566.
3. O’Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, et al. (2009) AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell 16: 401-412.
4. Whitesell L, Minnaugh E, de Costa B, Myers C, Neckers L. (1994) Inhibition of heat shock protein HSP90- p60 (v-src) heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation. Proc Nat Acad Sci USA 91: 8324-8328.
5. Ritossa F (1962) A new puffing pattern induced by temperature shock and DNP in drosophila. Experientia 18: 571-573.
6. Ellis RJ (2001) Macromolecular crowding: obvious but underappreciated. Trends Biochem Sci 26: 597-604.
7. Kampinga HH, Hageman J, Vos MJ, Kubota H, Tanguay RM, et al. (2009) Guidelines for the nomenclature of the human heat shock proteins. Cell Stress Chaperones 14: 105-111.
8. Bakua B , Weissman J, Horwich A (2006) Molecular chaperones and protein quality control. Cell 125: 443-451.
9. Hartl FU, Bracher A, Hayer-Hartl M (2011) Molecular chaperones in protein folding and proteinostasis. Nature 475: 324-332.
10. Ahmad A, Bhattacharya A, McDonald RA, Cordes M, Ellington B, et al. (2011) Heat shock protein 70 kDa chaperone/DnaJ cochaperone complex employs an unusual dynamic interface. Proc Nat Acad Sci USA 108: 18966-18971.
11. Hoffmann JM , Linke K, Graf PC, Lilie H, Jakob U (2004) Identification of a redox-regulated chaperone network. EMBO J 23: 160-168.
12. Neckers L, Workman P (2012) Hsp90 molecular chaperone inhibitors: are we there yet? Clin Cancer Res 18: 64-76.
13. Prodromou C, Roe SM, O’Brien R, Ladbury JE, Piper PW, et al. (1997) Identification and structural characterization of the ATP/ADP-binding site in the Hsp90 molecular chaperone. Cell 90: 65-75.
14. Pearl LH (2016) Review: The HSP90 molecular chaperone-an enigmatic ATPase. Biopolymers 105: 594-607.
15. Minnaugn EG, Xu W, Vos M, Yuan X, Isaacs JS, et al. (2004) Simultaneous inhibition of hsp 90 and the proteasome promotes protein ubiquitination,
causes endoplasmic reticulum-derived cytosolic vacuolization, and enhances antitumor activity. Mol Cancer Ther 3: 551-566.

16. Barrott JJ, Haystead TA (2013) Hsp90, an unlikely ally in the war on cancer. FEBS J 280: 1381-1396.

17. Whitesell L, Lindquist SL (2005) HSP90 and the chaperoning of cancer. Nat Rev Cancer 5: 761-772.

18. Simpson NE, Lambert WM, Watkins G, Giashuddin S, Huang SJ, et al. (2010) High levels of Hsp90 co-chaperone p23 promote tumor progression and poor prognosis in breast cancer by increasing lymph node metastases and drug resistance. Cancer Res 70: 8446-8456.

19. Reebye V, Querol Cano L, Lavery D, Brooke G, Powell S, et al. (2012) Role of the HSP90-associated co-chaperone p23 in enhancing activity of the androgen receptor and significance for prostate cancer. Molecular Endocrinology 26: 1694-1706.

20. Liu X, Zou L, Zhu L, Zhang H, Du C, et al. (2012) miRNA mediated up-regulation of co-chaperone p23 acts as an anti-apoptotic factor in childhood acute lymphoblastic leukemia. Leuk Res 36: 1098-1104.

21. Modi S, Stopeck A, Gordon M, Mendelson D, Solit D, et al. (2007) Combination of trastuzumab and trastuzumab-pertuzumab (17-AAG, KOS-953) is safe and active in trastuzumab-refractory HER-2-overexpressing breast cancer: a phase I dose-escalation study. J Clin Oncol 25: 5410-5417.

22. Zhang T, Hamza A, Cao X, Wang B, Yu S, et al. (2008) A novel Hsp90 inhibitor to disrupt Hsp90/Cdc37 complex against pancreatic cancer cells. Mol Cancer Ther 7: 162-170.

23. Patwardhan CA, Fauq A, Peterson LB, Miller C, Blagg BS, et al. (2013) Members of the heat-shock protein 70 family promote cancer cell growth by distinct mechanisms. Genes Dev 19: 570-582.

24. Ahmad A (2010) DnaK/DnaJ/GrpE of Hsp70 system have differing effects on alpha-synuclein fibrillation involved in Parkinson’s disease. Int J Biol Macromol 46: 275-279.

25. Rohe M, Daugaard M, Jensen MH, Helin K, Nylandsted J, et al. (2005) Crystal structure of the nucleotide exchange factor GrpE bound to the ATPase domain of the molecular chaperone DnaK. Science 276: 431-435.

26. Gedunin inactivates the co-chaperone p23 protein causing cancer cell death by apoptosis. J Biol Chem 288: 7313-7325.

27. Garcia-Carbonero R, Carnero A, Paz-Ares L (2013) Inhibition of HSP90 molecular chaperones: moving into the clinic. Lancet Oncol 14: e358-369.

28. Harrison CJ, Hayer-Hartl M, Di Liberto M, Hartl F, Kuriyan J (1997) Heat shock protein (Hsp) 70 and Hsp 40 in colorectal cancer. Medical & Cellular Biology 29: 559-569.

29. Harrison CJ, Hayer-Hartl M, Di Liberto M, Hartl F, Kuriyan J (1997) Heat shock protein (Hsp) 70 and Hsp 40 in colorectal cancer. Medical & Cellular Biology 29: 559-569.

30. Rohde M, Daugaard M, Jensen MH, Helin K, Nylandsted J, et al. (2005) Members of the heat-shock protein 70 family promote cancer cell growth by distinct mechanisms. Genes Dev 19: 570-582.

31. Ahmad A (2010) DnaK/DnaJ/GrpE of Hsp70 system have differing effects on alpha-synuclein fibrillation involved in Parkinson’s disease. Int J Biol Macromol 46: 275-279.

32. Ciocca DR, Arrigo AP, Calderwood SK (2013) Heat shock proteins and heat shock factor 1 in carcinogenesis and tumor development: an update. Arch Toxicol 87: 19-48.

33. Wadhwa R, Taira K, Kaul SC (2002) An Hsp70 family chaperone, mortalin/mthsp70/PBP74/Grp75: what, when, and where? Cell Stress Chaperones 7: 309-316.

34. Li X, Srinivasan S, Tillekeratne M, Shou W, Sanchez E (2007) Analysis of heat shock protein (Hsp) 70 and Hsp 40 in gastric cancer. Cancer Lett 198: 219-228.

35. Kanazawa Y, Isomoto H, Oka M, Yano Y, Kanazawa H, et al. (2003) Expression of heat shock protein (Hsp) 70 in prostate cancer. Cancer Lett 198: 219-228.

36. Kanazawa Y, Isomoto H, Oka M, Yano Y, Yano Y, et al. (2003) Expression of heat shock protein (Hsp) 70 in colorectal cancer. Medical Oncology 20: 157-164.

37. Dai C, Whitesell L, Rogers AB, Lindquist S (2007) Heat shock factor 1 is a powerful multifaceted modifier of carcinogenesis. Cell 130: 1005-1018.

38. Khaledi M, Bhati A, Gong J, Gray P, Schade V, et al. (2008) Heat shock factor 1 represses estrogen-dependent transcription through association with MTA1. Oncogene. 27: 1886-1893.

39. Santagata S, Ha R, Lin NU, Mendillo ML, Collins LC, et al. (2011) High levels of nuclear heat-shock factor 1 (HSF1) are associated with poor prognosis in breast cancer. Proc Natl Acad Sci U S A 108: 18378-18383.

40. Gabai V, Yaglom I, Waldman T, Sherman M (2009) Heat shock protein Hsp72 controls oncogene-induced senescence pathways in cancer cells. Molecular and Cellular Biology 29: 559-569.

41. Powers MV, Clarke PA, Workman P (2008) Dual targeting of HSC70 and HSP72 inhibits HSP90 function and induces tumor-specific apoptosis. Cancer Cell 14: 250-262.

42. Saluja A, Dudeva V (2008) Heat shock proteins in pancreatic diseases. J Gastroenterol Hepatol 23: 542-45.

43. Yi X, Luk JM, Lee NP, Peng J, Leng X, et al. (2008) Association of Mortalin (HSP99) with Liver Cancer Metastasis and Prediction for Early Tumor Recurrence. Molecular & Cellular Proteomics 7: 315-325.

44. Cesa L, Patury S, Komiyama T, Ahmad A, Zuidweg E, et al. (2013) Inhibitors of difficult protein-protein interactions identified by high-throughput screening of multiprotein complexes. American Chemical Society Chemical Biology 8: 1988-1997.

45. Li X, Srinivasan S, Connarn J, Ahmad A, Young Z, et al. (2013) Analogs of the Allosteric Heat Shock Protein 70 (Hsp70) Inhibitor, MKT-077, as Anti-Cancer Agents. American Chemical Society Medicinal Chemistry Letters 4: 1042-1047.

46. Periyasamy S, Warrier M, Tillekeratne M, Shou W, Sanchez E (2007) The immunophilin ligands cyclosporin A and FK506 suppress prostate cancer cell growth by androgen receptor-dependent and -independent mechanisms. Endocrinology 148: 4716-4726.

47. Kumar P, Mark PJ, Ward BK, Minchin RF, Ratajczak T (2001) Estradiol-regulated expression of the immunophilins cyclophilin A and FKBP52 in MCF-7 breast cancer cells. Biochem Biophys Res Commun 284: 219-225.