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# Distinct prognostic roles of *HSPB1* expression in non-small cell lung cancer

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Lung cancer is the leading cause of cancer morbidity and mortality around world. Heat shock protein beta-1 (HSPB1) expression is aberrantly increased in non-small cell lung cancer (NSCLC) patients. However, the roles of *HSPB1* expression in the prognosis of NSCLC are still elusive. In this study, we investigated the prognostic roles of HSPB1 in NSCLC by using "The Kaplan-Meier plotter" (KM plotter) database. Our data indicated that *HSPB1* mRNA low expression was correlated to better overall survival (OS) for all NSCLC patients, hazard ratio (HR) 1.41 (1.24–1.61), p=1.1e-7, and better OS in lung adenocarcinoma (LUAD) patients, HR 1.81 (1.42–2.32), p=1.5e-06, but not in lung squamous cell carcinoma (LUSC) patients, HR 1.21 (0.94–1.55), p=0.14. In addition, mRNA low expression of *HSPB1* is also significantly associated with better OS of NSCLC patients in different smoking status, in different chemotherapy status, in clinical stage I & II, as well as patients with successful surgery treatment. Our results indicated that *HSPB1* expression may have distinct prognostic values in NSCLC patients, and may provide an effective clinical strategy to accurately predict the prognosis of NSCLC patients.

*Key words: HSPB1, NSCLC, KM plotter, prognostic roles*

Lung cancer (LC) is the most common causes of cancer induced deaths in China and worldwide [1]. The 5-year survival rate of LC is very low, which is below 50% in patients with early-stage cancer and is less than 5% in patients with advanced-stage cancer [2]. And the prognosis of LC is also very poor. Non-small cell lung carcinoma (NSCLC), accounting ~85% of LC associated mortalities worldwide [1], includes two major types, lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). Although, remarkable progress in LC treatment has been made recently, only limited efforts have been made in comprehensive to identify potential prognostic markers and potential drug targets of lung cancer patients, especially in NSCLC. Therefore, it is critical to develop a more accurate prognostic assessment and molecular biomarkers for NSCLC.

*HSPB1* (heat shock protein beta-1) is a gene coding the protein called heat shock protein beta-1 (HSPB1), which is also called heat shock protein 27 (HSP27) [3]. Accumulated evidences indicated that HSPB1 was involved in the pathogenesis of various cancers [4–6]. HSPB1 was highly expressed in mouse lung cancer tissues and stimulated cell proliferation through activator protein-1 (AP-1) related pathway [7]. In hepatocellular carcinoma (HCC) patients, the high expression of HSPB1 indicated poor prognosis [6]. And in prostate cancer and colon cancer patients, the HSPB1 is critical to the initiation of chemoresistance [8]. However, there are no reports on the prognostic roles of HSPB1 in NSCLC patients.

The Cancer Genome Atlas (TCGA) is a project supervised by the National Cancer Institute's Center and the National Human Genome Research Institute funded by the US government from 2005. By using the genome sequencing and bioinformatics approaches, TCGA catalogues genetic mutations responsible for various cancers, and this provides a rich source for investigators to analyze the potential mechanism of cancer pathogenesis. The "Kaplan-Meier plotter" (KM plotter), established using the gene expression data and relapse free and overall survival information downloaded from TCGA, as well as The European Genome-phenome Archive (EGA) and Gene Expression Omnibus (GEO) [9]. KM plotter has been reported to analyze the prognostic value of a particular gene and potential drug targets in NSCLC and other cancers [10–14]. Here, we used KM plotter database to investigate the prognostic roles of *HSPB1* expression in NSCLC patients.

## Materials and methods

To analysis the prognostic roles of *HSPB1* expression in NSCLC, we used a public database to study the relevance and significance of the mRNA level of *HSPB1* to overall survival (OS) in different analysis section. The data from NSCLC patients used for KM plotter analysis were pooled from The Cancer Genome Atlas (TCGA, http://cancergenome.nih.gov), Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) and Cancer Biomedical Informatics Grid (caBIG, https://biospecimens.cancer.gov/relatedinitiatives/overview/caBig.asp) [15]. And the whole database included the gene expression (most of samples including the mRNA level) and survival information (20 years) from 1928 NSCLC patients.

To obtain Kaplan-Meier plots for the patients OS rate, we used the KM plotter, and *HSPB1* was entered into the database (http://kmplot.com/analysis/index.php?p=service&cancer=lung). And the number-at-risk displayed under the main panel of the OS. Based on the expression of *HSPB1*, the patients were divided into two groups. Patients with *HSPB1* expression higher than the median separates were pooled into the group with high expression, while the patients with *HSPB1* expression lower than the median separates were pooled into the group with low expression. Other statistic outcomes, including hazard ratio (HR), 95% confidence intervals and log rank P, calculated from the database were also included in the figures and tables in this manuscript. Values of $p<0.05$ were used to indicate a statistically significant difference [16].

## Results

We used KM plotter and determined the prognostic value of *HSPB1* in the database. The Affymetrix IDs is valid: 201841_s_at (*HSPB1*). Survival curves are drafted for all NSCLC patients (n=1,926) (Figure 1A), for LUAD patients (n=720) (Figure 1B), and for LUSC patients (n=524) (Figure 1C). *HSPB1* mRNA low expression was correlated to better overall survival (OS) for all NSCLC patients who were followed for 20 years, hazard ratio (HR) 1.41 (1.24–1.61),

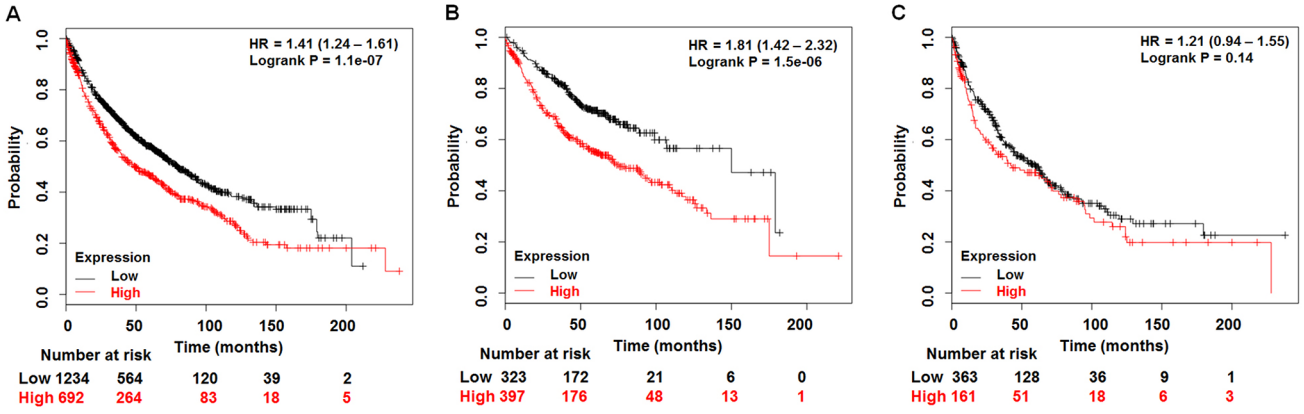


**Figure 1. Prognostic value of *HSPB1* expression in the database. The Affymetrix IDs is valid: 201841_s_at (*HSPB1*). A) Survival curves are plotted for all NSCLC patients (n=1,926). B) Survival curves are plotted for adenocarcinoma patients (n=720). C) Survival curves are plotted for squamous cell carcinoma patients (n=524).**

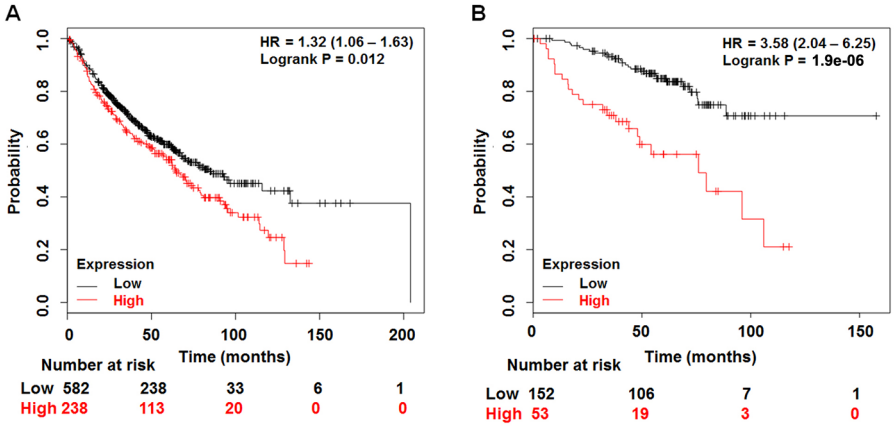


**Figure 2. Prognostic value of *HSPB1* mRNA expression in smoked patients and never smoked patients. The Affymetrix IDs is valid: 201841_s_at (*HSPB1*). A) Survival curves are plotted for all smoked patients (n=820).B) Survival curves are plotted for all never smoked patients (n=205).**

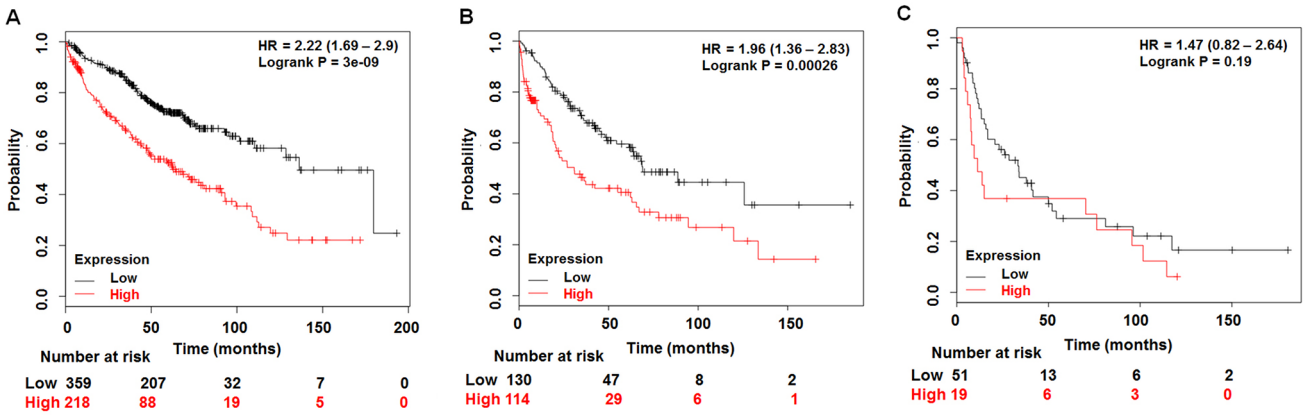


**Figure 3. Prognostic value of *HSPB1* mRNA expression in NSCLC patients in different stages. The Affymetrix IDs is valid: 201841_s_at (*HSPB1*). A) Survival curves are plotted for patients in stage 1 (n=577).B) Survival curves are plotted for patients in stage 2 (n=244). C) Survival curves are plotted for patients in stage 3 (n=70).**

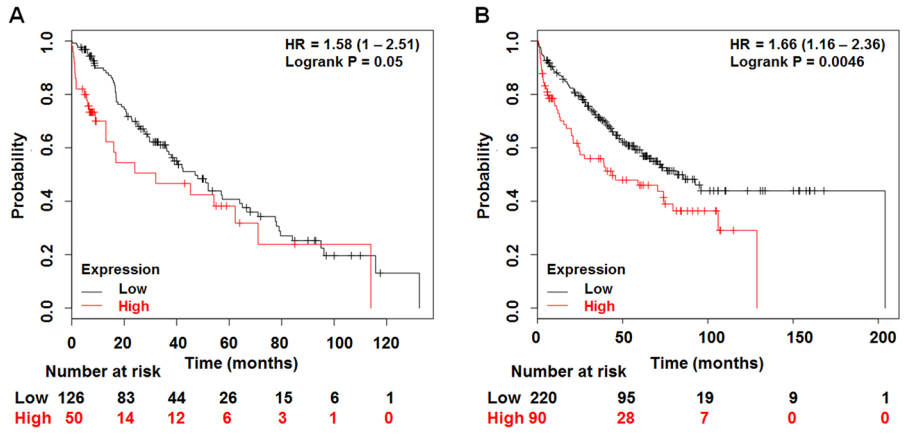


**Figure 4. Determination of prognostic value of *HSPB1* expression in NSCLC patients with or without chemotherapy. The Affymetrix IDs is valid: 201841_s_at (*HSPB1*). A) Survival curves are plotted for patients with chemotherapy (n=176). B) Survival curves are plotted for patients without chemotherapy (n=310).**

p=1.1e-7. *HSPB1* mRNA low expression was also correlated to better OS in LUAD patients, HR 1.81 (1.42–2.32), p=1.5e-06, but not in LUSC patients, HR 1.21 (0.94–1.55), p=0.14.

For further assess the association of *HSPB1* with other clinicopathological profiles, we determined the correlation with the patients' smoking status (Table 1, Figure 2), different clinical stages (Table 2, Figure 3), different chemotherapeutic treatments (Table 3, Figure 4) and different surgical treatments (Table 4, Figure 5). As shown in Figure 2 and Table 1, *HSPB1* mRNA low expression was correlated to better OS in smoked patients HR 1.32 (1.06–1.63), p=0.0123 (Figure 2A) and in never smoked patients HR 3.58 (2.04–6.25), p=1.9e-06 (Figure 2B). As shown in Figure 3 and Table 2, *HSPB1* mRNA low expression was correlated to better OS in stage I patients HR 2.22 (1.69–2.9), p=3e-9 (Figure 3A) and stage II patients HR 1.96 (1.36–2.83), p=0.0003 (Figure 3B). And the *HSPB1* mRNA low expression was also marginally correlated to better OS in patients with chemotherapeutic treatment HR 1.58 (1–2.51), p=0.0522 (Figure 4A) and significantly corre-

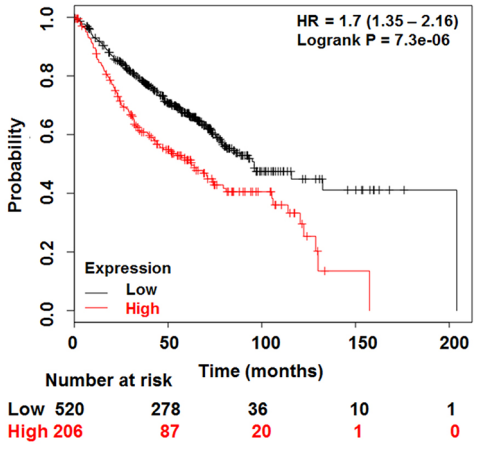


**Figure 5. Prognostic value of *HSPB1* mRNA expression in NSCLC patients with surgery. The Affymetrix IDs is valid: 201841_s_at (*HSPB1*). Survival curves are plotted for patients after surgery only with negative surgical margins (n=726).**

**Table 1. Correlation of *HSPB1* mRNA expression with smoking status of NSCLC patients.**

| Smoking status | Cases | HR | 95% CI | p-value |
|---|---|---|---|---|
| Never smoked | 205 | 3.58 | 2.04–6.25 | 1.9e-6 |
| Smoked | 820 | 1.32 | 1.06–1.63 | 0.0123 |

**Table 2. Correlation of *HSPB1* mRNA expression with clinical stages of NSCLC patients.**

| Clinical stages | Cases | HR | 95% CI | p-value |
|---|---|---|---|---|
| I | 677 | 2.22 | 1.69–2.9 | 3e-9 |
| II | 244 | 1.96 | 1.36–2.83 | 0.0003 |
| III | 70 | 1.47 | 0.82–2.64 | 0.1918 |

**Table 3. Correlation of *HSPB1* mRNA expression with chemotherapy of NSCLC patients.**

| Chemotherapy | Cases | HR | 95% CI | p-value |
|---|---|---|---|---|
| No | 310 | 1.66 | 1.16–2.36 | 0.0046 |
| Yes | 176 | 1.58 | 1–2.51 | 0.0522 |

**Table 4. Correlation of *HSPB1* mRNA expression in NSCLC patients with negative surgical margins.**

| Cases | HR | 95% CI | p-value |
|---|---|---|---|
| 726 | 1.7 | 1.35–2.16 | 7.3e-6 |

lated to better OS in patients without chemotherapy HR 1.66 (1.16–2.36), p=0.0046 (Figure 4B). From Table 4, *HSPB1* is significantly correlated to the patients with successful surgery treatment. As shown in Figure 5, *HSPB1* mRNA low expression was correlated to better OS in patients with negative surgical margins HR 1.7 (1.35–2.16), p=7.3e-6.

## Discussion

Heat shock proteins (HSPs) are produced by cells and tissues in response to various stressful conditions, including cold [17], UV light [18], wound healing or tissue remodeling [19]. Recently, accumulated evidences indicated that HSPs are aberrantly overexpressed in many types of human cancers and play critical roles in tumor progression. HSPs are involved in the cancer cell differentiation, proliferation, metastasis and invasion [20]. HSPB1 is one of important components in HSP family [21]. Recent studies have indicated that the expression of HSPB1 is associated with poor prognosis of a wide range of human cancers [20, 22], including gastric [23], osteosarcomas [24], prostate [25, 26] and liver carcinoma [27]. However, the prognostic roles of *HSPB1* in NSCLC have not been studied.

HSPB1 is expressed at high levels in breast cancer [28], HCC cancer [6, 27] and prostate cancer [4, 8], and it is essential for tumor development through different mechanisms. In breast cancer cells, HSPB1 was required for cell migration and cancer stem cell maintenance, which may through the interaction of NF-κB dependent pathway [28]. And the phosphorylated HSPB1, which is formed through the kinases catalyzed phosphorylation of HSPB1, is essential to the progression of various cancers. Recently, phosphorylated HSPB1 has been proved to suppress apoptosis, enhance invasion and survival in cancer cells [29]. Additionally, recent studies indicated that phosphorylation of HSPB1 could modify the subcellular localization of HSPB1 in HCC cells [30]. And abolish the phosphorylation of HSPB1 through mutating the phosphorylation site from serine residues to alanine residues blocks the phosphorylation of HSPB1 and attenuates the translocation of HSPB1 to nuclei in HCC cells, and suggested that the subcellular localization of HSPB1 may play essential biological roles in liver cancer [30]. Accumulating evidence links rising HSPB1 expression levels with the progression of prostate cancer [31]. In prostate cancer cells, HSPB1 has been shown to bind with androgen and androgen receptor to form a complex, and induced the activation of androgen receptor, stimulated translocation of the complex to nuclei and further regulated gene expression and tumor progression [31].

Recent investigation indicated that the protein expression of *HSPB1* was increased in the mouse lung tissue with lung cancer [7], and predicted the relationship between the expression of HSPB1 and lung cancer progression. In this study, we investigated the prognostic values of *HSPB1* expression in NSCLC patients through analyzing the OS of NSCLC patients by using the KM plotter database. Our current studies indicated that *HSPB1* is a predictor of NSCLC prognosis, and it is functional as an oncogene during NSCLC progression. The NSCLC patients with high expression of HSPB1 associated with the poor OS. And recent investigations in animal models and cell culture system also suggested that *HSPB1* expression is associated with the tumor progression in various human cancers. Molecular biological investigations to study the expression of *HSPB1* in tumor tissues and cells from human cancer patients have proved that the expression of *HSPB1* is significantly higher in tumor tissues than control tissues from human hepatocellular carcinoma [6] and prostate cancer [4, 8, 32] and mouse lung cancer [7]. In human hepatocellular carcinoma, *HSPB1* stimulates tumor progression through facilitating the hepatocellular carcinoma cells metastasis via Akt signaling [6, 22]. Both in vivo and in vitro studies of the prostate cancer indicated that *HSPB1* regulates human prostate cancer cell motility and metastatic progression via increased the expression of matrix metalloproteinase 2 (MMP-2) [29], which is a key stimulator for cancer cell invasion [33]. In mouse lung cancer development, *HSPB1* was proved to induce the lung cancer cells proliferation via activator protein-1 (AP-1) dependent pathway [7]. Additionally, *HSPB1* also plays critical roles to the initiation of the chemotherapeutic resistance in prostate cancer [8] and colon cancer [34], and this may through the

phosphorylation of HSPB1 protein. Notably, the HSPB1 inhibitor, OGX-427, has been used as a drug candidate to treat the patients with castration-resistant prostate cancer and other advanced cancers [32]. Together, HSPB1 was proved to involve in the tumor progression in various kinds of cancers, and its inhibitor would be a potential therapy to patient with advanced cancers.

In conclusion, our investigations demonstrated the distinct prognostic roles of *HSPB1* mRNA expression in patients with NSCLC, and *HSPB1* mRNA low expression was correlated to better OS for all NSCLC patients and in LUAD patients, but not in LUSC patients. Thus, our results suggested that *HSPB1* might be potential drug target for NSCLC patients, and its expression may have distinct prognostic values in NSCLC patients.

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## References

[1] MOLINA JR, YANG P, CASSIVI SD SCHILD SE, ADJEI AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008; 83: 584–594. doi: 10.4065/83.5.584

[2] CRINO L, WEDER W, VAN MEERBEECK J FELIP E; ESMO GUIDELINES WORKING GROUP. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5: v103–115. doi: 10.1093/annonc/mdq207

[3] BATULAN Z, PULAKAZHI VENU VK, LI Y, KOUMBADINGA G, ALVAREZ-OLMEDO DG et al. Extracellular Release and Signaling by Heat Shock Protein 27: Role in Modifying Vascular Inflammation. Front Immunol 2016; 7: 285. doi: 10.3389/fimmu.2016.00285

[4] ANDRIEU C, TAIEB D, BAYLOT V, ETTINGER S, SOUBEYRAN P et al. Heat shock protein 27 confers resistance to androgen ablation and chemotherapy in prostate cancer cells through eIF4E. Oncogene 2010; 29: 1883–1896. doi: 10.1038/onc.2009.479

[5] KIM J, JUNG H, LIM W, KIM S, KO Y et al. Down-regulation of heat-shock protein 27-induced resistance to photodynamic therapy in oral cancer cells. J Oral Pathol Med 2013; 42: 9–16. doi: 10.1111/j.1600-0714.2012.01155.x

[6] ZHANG Y, TAO X, JIN G, JIN H, WANG N et al. A Targetable Molecular Chaperone Hsp27 Confers Aggressiveness in Hepatocellular Carcinoma. Theranostics 2016; 6: 558–570. doi: 10.7150/thno.14693

[7] ZHANG S, HU Y, HUANG Y, XU H, WU G et al. Heat shock protein 27 promotes cell proliferation through activator protein-1 in lung cancer. Oncol Lett 2015; 9: 2572–2576. doi: 10.3892/ol.2015.3073

[8] STOPE MB, WEISS M, PREUSS M, STREITBORGER A, RITTER CA et al. Immediate and transient phosphorylation of the heat shock protein 27 initiates chemoresistance in prostate cancer cells. Oncol Rep 2014; 32: 2380–2386. doi: 10.3892/or.2014.3492

[9] BAI Y, LI LD, LI J, LU X. Targeting of topoisomerases for prognosis and drug resistance in ovarian cancer. J Ovarian Res 2016; 9: 35. doi: 10.1186/s13048-016-0244-9

[10] ORTEGA CE, SEIDNER Y, DOMINGUEZ I. Mining CK2 in cancer. PLoS One 2014; 9: e115609. doi: 10.1371/journal.pone.0115609

[11] XIONG J, ZHANG X, CHEN X, WEI Y, LU DG et al. Prognostic roles of mRNA expression of notch receptors in non-small cell lung cancer. Oncotarget 2017; 8: 13157–13165. doi: 10.18632/oncotarget.14483

[12] XIA P, XU XY. Prognostic significance of CD44 in human colon cancer and gastric cancer: Evidence from bioinformatic analyses. Oncotarget 2016; 7: 45538–45546. doi: 10.18632/oncotarget.9998

[13] OCANA A, PEREZ-PENA J, ALCARAZ-SANABRIA A, SÁNCHEZ-CORRALES V, NIETO-JIMÉNEZ C et al. In silico analyses identify gene-sets, associated with clinical outcome in ovarian cancer: role of mitotic kinases. Oncotarget 2016; 7: 22865–22872. doi: 10.18632/oncotarget.8118

[14] HERNANDEZ SJ, DOLIVO DM, DOMINKO T. PRMT8 demonstrates variant-specific expression in cancer cells and correlates with patient survival in breast, ovarian and gastric cancer. Oncol Lett 2017; 13: 1983–1989. doi: 10.3892/ol.2017.5671

[15] GYORFFY B, SUROWIAK P, BUDCZIES J, LANCZKY A. Online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in non-small-cell lung cancer. PLoS One 2013; 8: e82241. doi: 10.1371/journal.pone.0082241

[16] HUANG LS, MATHEW B, LI H, ZHAO Y, MA SF et al. The mitochondrial cardiolipin remodeling enzyme lysocardiolipin acyltransferase is a novel target in pulmonary fibrosis. Am J Respir Crit Care Med 2014; 189: 1402–1415. doi: 10.1164/rccm.201310-1917OC

[17] MATZ JM, BLAKE MJ, TATELMAN HM, LAVOI KP, HOLBROOK NJ. Characterization and regulation of cold-induced heat shock protein expression in mouse brown adipose tissue. Am J Physiol 1995; 269: R38–47

[18] CAO Y, OHWATARI N, MATSUMOTO T, KOSAKA M, OHTSURU A et al. TGF-beta1 mediates 70-kDa heat shock protein induction due to ultraviolet irradiation in human skin fibroblasts. Pflugers Arch 1999; 438: 239–244.

[19] LAPLANTE AF, MOULIN V, AUGER FA, LANDRY J, LI H et al. Expression of heat shock proteins in mouse skin during wound healing. J Histochem Cytochem 1998; 46: 1291–1301. doi: 10.1177/002215549804601109

[20] CIOCCA DR, CALDERWOOD SK. Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones 2005; 10: 86–103.

[21] PURANDHAR K, JENA PK, PRAJAPATI B, RAJPUT P, SESHADRI S. Understanding the role of heat shock protein isoforms in male fertility, aging and apoptosis. World J Mens Health 2014; 32: 123–132. doi: 10.5534/wjmh.2014.32.3.123

[22] ARRIGO AP, GIBERT B. HspB1, HspB5 and HspB4 in Human Cancers: Potent Oncogenic Role of Some of Their Client Proteins. Cancers (Basel) 2014; 6: 333–365. doi: 10.3390/cancers6010333

[23] KAPRANOS N, KOMINEA A, KONSTANTINOPOULOS PA, SAVVA S, ARTELARIS S et al. Expression of the 27-kDa heat shock protein (HSP27) in gastric carcinomas and adjacent normal, metaplastic, and dysplastic gastric mucosa, and its prognostic significance. J Cancer Res Clin Oncol 2002; 128: 426–432. doi: 10.1007/s00432-002-0357-y

[24] TRIEB K, LECHLEITNER T, LANG S, WINDHAGER R, KOTZ R et al. Heat shock protein 72 expression in osteosarcomas correlates with good response to neoadjuvant chemotherapy. Human Pathol 1998; 29: 1050–1055.

[25] ROCCHI P, SO A, KOJIMA S, SIGNAEVSKY M, BERALDI E et al. Heat shock protein 27 increases after androgen ablation and plays a cytoprotective role in hormone-refractory prostate cancer. Cancer Res 2004; 64: 6595–6602. doi: 10.1158/0008-5472.CAN-03-3998

[26] WANG Y, THERIAULT JR, HE H, GONG J, CALDERWOOD SK. Expression of a dominant negative heat shock factor-1 construct inhibits aneuploidy in prostate carcinoma cells. J Biol Chem 2004; 279: 32651–32659. doi: 10.1074/jbc.M401475200

[27] ROMANI AA, CRAFA P, DESENZANI S, GRAIANI G, LAGRASTA C et al. The expression of HSP27 is associated with poor clinical outcome in intrahepatic cholangiocarcinoma. BMC Cancer 2007; 7: 232. doi: 10.1186/1471-2407-7-232

[28] WEI L, LIU TT, WANG HH, HONG HM, YU AL et al. Hsp27 participates in the maintenance of breast cancer stem cells through regulation of epithelial-mesenchymal transition and nuclear factor-kappaB. Breast cancer research : Breast Cancer Res 2011; 13: R101. doi: 10.1186/bcr3042

[29] KATSOGIANNOU M, ANDRIEU C, ROCCHI P. Heat shock protein 27 phosphorylation state is associated with cancer progression. Front Genet 2014; 5: 346. doi: 10.3389/fgene.2014.00346

[30] GUO K, GAN L, ZHANG S, CUI FJ, CUN W et al. Translocation of HSP27 into liver cancer cell nucleus may be associated with phosphorylation and O-GlcNAc glycosylation. Oncol Rep 2012; 28: 494–500. doi: 10.3892/or.2012.1844

[31] ALBANY C, HAHN NM. Heat shock and other apoptosis-related proteins as therapeutic targets in prostate cancer. Asian J Androl 2014; 16: 359–363. doi: 10.4103/1008-682X.126400

[32] CHI KN, YU EY, JACOBS C, BAZOV J, KOLLMANNSBERGER et al. A phase I dose-escalation study of apatorsen (OGX-427), an antisense inhibitor targeting heat shock protein 27 (Hsp27), in patients with castration-resistant prostate cancer and other advanced cancers. Ann Oncol 2016; 27: 1116–1122. doi: 10.1093/annonc/mdw068

[33] VOLL EA, OGDEN IM, PAVESE JM, HUANG X, XU L et al. Heat shock protein 27 regulates human prostate cancer cell motility and metastatic progression. Oncotarget 2014; 5: 2648–2663. doi: 10.18632/oncotarget.1917

[34] TSURUTA M, NISHIBORI H, HASEGAWA H, ISHII Y, ENDO T et al. Heat shock protein 27, a novel regulator of 5-fluorouracil resistance in colon cancer. Oncol Rep 2008; 20: 1165–1172