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ORIGINAL ARTICLE

Collagen-specific chaperone, heat shock protein 47 kDa (HSP47)–pathway and expression patterns in cancer

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ABSTRACT

Background: Human serpin gene *SERPINH1* encodes for a non-inhibitory serpin shock protein 47 kDa (HSP47) a client-specific chaperone, which is a hallmark in the collagen biosynthesis. Till today, there is no comprehensive study on the protein network for human HSP47. Thus, the current study aimed at studying the pathway and expression patterns observed in collagen-specific chaperone, HSP47 in relation to cancer.

Methodology: The study used STRING 10 (http://version10a.string-db.org) in finding putative protein interaction partners of human HSP47. Also, database HMMER3 (www.hmmer.org/) with Pfam 32.0 (September 2018) dataset was used in identifying Pfam protein domains from proteins interacting with HSP47. The dbDEPC3.0 was used for the evaluation of expression patterns of HSP47 in different cancer. Further three online resources, namely, human protein atlas (https://www.proteinatlas.org/), genotype-tissue expression (https://gtexportal.org), and FANTOM5 project (http://fantom.gsc.riken.jp/5/) was used to examine HSP47 expression in normal human tissues.

Results: Upon constructing protein interactive map of human HSP47, the study found that a set of molecular chaperones as interaction partners of HSP47, which included two copies each of cAMP response element binding proteins, HSP27, HSP40, HSP70, HSP90, ubiquitin proteins and one copy each of cartilage associated protein, HSPH1, HSBP1, FK506-binding protein 4, kruppel-like factor, peptidyl-prolyl isomerase, and Prolyl 4-hydroxylase beta subunit.

Conclusion: The study found a cocktail of different chaperones interacting with HSP47, originated at different time points from prokaryotes to eukaryotes. Overall, the study was successful in finding HSP47 expression patterns among several normal tissues using three different publicly available datasets. It also assessed the expression pattern of HSP47 in human cancer types. These findings will encourage further studies focusing on the role of HSP47 in human diseases.

Keywords: HSP47, SERPINH1, protein-protein interaction, cancer, expression patterns.

Introduction

Heat shock protein 47 kDa (HSP47) serves as an endoplasmic reticulum (ER)-residing collagen-specific chaperone and has the cavalier role in collagen biosynthesis and its structural assembly process (1,2). HSP47 protein is the product of the human *SERPINH1* gene, which belongs to the group V6 in the indel-based group-wise classification of vertebrate serpins (3). Structurally, HSP47 is a typical serpin domain (Pfam ID—PF00079), composed of three β-sheets (*s*) and nine α-helices (*h*) as sA-sC and hA-hI, respectively (4). HSP47 has a non-inhibitory reactive center loop (1). Previous reports have mainly focused on the role of HSP47 in the collagen biosynthesis and in exploring its evolutionary history (1). Human HSP47 has been reported to be associated with several human diseases, including familial connective tissue disorder Osteogenesis imperfecta (OI) (5) and various types of cancer (6). Till today, there has been no study conducted exclusively in studying the

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protein interactome of HSP47. To resolve this issue, the current study team has constructed interaction maps of HSP47 to identify the top 20 interactions partners, most of which include heat shock proteins. The study team also examined the expression pattern of HPS47 in the different types of cancer and normal tissues.

Materials and Methods

The putative protein interaction partners of human HSP47 was detected using online database STRING 10 (website: http://version10a.string-db.org (7)) with confidence score higher than 0.9 with searching options of top 20 interaction partners. The study identified Pfam protein domains from proteins interacting with HSP47 using HMMER3 with Pfam 32.0 (September 2018) dataset. Evaluation of HSP47 expression in different cancers tissues and normal tissues was performed using dbDEPC 3.0, the database of differential expression of the protein in cancer (8). The current study also examined HSP47 expression in normal human tissues using three online resources, namely, human protein atlas (HPA, https://www.proteinatlas.org/), genotype-tissue expression (GTEx, https://gtexportal.org), and FANTOM5 project (http://fantom.gsc.riken.jp/5/).

Results and Discussion

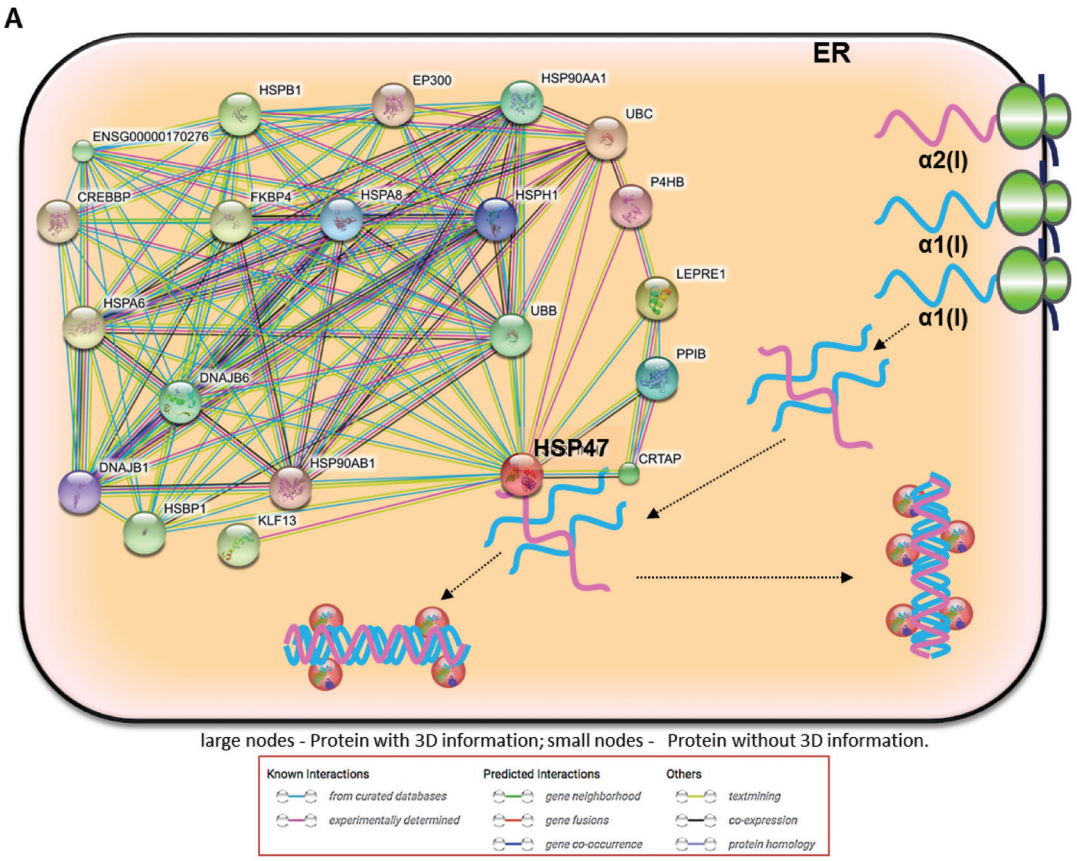
A cocktail of different chaperones interacts with HSP47

To evaluate the protein interaction partners of HSP47, the study team constructed the interactome map of human HSP47 protein. Remarkably top 20 protein–protein interaction partners (confidence score ≥ 0.9) were found to be different types of molecular chaperones (Figure 1; Table 1). This suggested that a cocktail of different molecular chaperones is essential for maintaining proper physiology of HSP47 in the ER. On plotting these proteins on the evolutionary scale, it was evident that these partners are originated at different time points (Figure 2). Furthermore, three of these proteins were found to be highly conserved across different evolutionary lineages (marked by the green box in Figure 2).

HSP47 interaction partners have protein domain level similarities

These HSP47 interaction partners include two paralogs involved in histone acetylating process: cAMP response element binding (CREB) binding protein (CREBBP) and E1A binding protein p300 (EP300) (9). These two proteins were closely related in size where CREBBP and EP300 were 2,442 and 2,414 residues long, respectively. These two proteins were also found to possess multiple Pfam domains, such as Zf-TAZ (Pfam ID—PF02135.15), KIX (PF02172.15), Bromo (PF00439.24), unknown domain (PF06001.12), HAT_KAT11 (PF08214.10), ZZ (PF00569.16), and other unknown domain (PF09030.9), respectively (Figure 3A–B). Both CREBBP and EP300 proteins work as histone acetyltransferases and are involved in transcription regulation and/or cell cycle progression by modulating the chromatin structure (9). Furthermore, they also act as prominent chromatin remodelers operating as scaffolds, which stabilize other protein–protein partners with the formation of transcription complexes. Both of them are also involved in crucial physiological roles, including development, growth, and homeostasis (9). *CREBBP* and *EP300* genes are localized in the human genome (Table 1) on the chromosomes 16 (cytoplasmic band 16p13.3) and 22 (22q13.2), respectively. Mutations in these genes cause a rare neurodevelopmental syndrome known as the Rubinstein–Taybi syndrome (RSTS, OMIM #180849, #613684), which is characterized by deformity in facial appearance, skeletal and dysmorphic abnormalities, microcephaly, enlargement of thumbs and first toes, and impaired intellectual and postnatal growth (10). Cartilage associated protein (CRTAP) reported was 401 amino acids long without any known protein domain (Figure 3C). It is encoded by the *CRTAP* gene localized on the human chromosome 3 (cytoplasmic band 3p22.3, Table 1). CRTAP forms the collagen prolyl 3-hydroxylation complex with P3H1 and cyclophilin B (CyPB) in the ER, which 3-hydroxylates the pro986 residue of α1(I) and α1(II) collagen chains (11). CRTAP is also associated with a small percentage (5%–7%) of patients with severe to lethal OI types VII (OMIM #610682). Five known mutations are reported in *the CRTAP* gene, leading into either prevention of the production of any cartilage associated proteins, or reduction in the production of cartilage associated proteins. Irregularities in the production of cartilage associated proteins cause problems information of collagen, which ultimately results in the severe form of OI (11).There have been two HSP40 proteins found to be involved in HSP47 interaction, including DnaJ (Hsp40) homolog subfamily B member 1 (DNAJB1) and member 6 (DNAJB6) of residue size of 326 and 340. DNAJB1 possesses two protein domains as DnaJ (PF00226. 31) in the N-terminal end (4–65 residues) and DnaJ_C (PF01556.18) in the C-terminal end (164–323 residues), while DNAJB6 only harbors DnaJ (PF00226.31) in the N-terminal end (3–66) (Figure 3D and E). These two proteins are encoded by genes *DNAJB1* and *DNAJB6*, respectively, and these genes are localized on human chromosomes 19 (19p13.12) and 7 (7q36.3) (Table 1). J-domain is highly conserved domains amongst hsp40 proteins, which is associated with protein folding and protein disaggregation along with HSP70 (12,13). These two proteins are associated with human diseases resulted due to impaired protein folding (14,15). FK506-binding protein 4 (FKBP4) is 59 kDa immunophilin protein. FKBP4 protein is 459 amino acids long composed of two FKBP_C (PF00254.28) domains in the regions of 44–134 and 162–249 residues and two tetratricopeptide repeat domains [tetratricopeptide repeat (TPR)_1, PF00515.28, and TPR_2, PF07719.17] in the regions of 321–352 and 354–386 (Figure 3F). These TPRs are

required for interactions with HSP70 and HSP90 as co-chaperones (16). FKBP4 is majorly involved in protein folding and cellular trafficking (16). This protein is encoded by *FKBP4* gene mapped in the region of 12p13.33 on human chromosome 12 (Table 1). There are two HSP70 homologs as interaction partners of HSP47 as heat shock 70kDa protein 6 (HSPA6) and HSPA8 (also known as heat shock cognate 71 kDa protein, Hsc70), both of these proteins harbor HSP70 (PF00012.19) protein domain (Figure 3G and H). These two proteins



B

		Neighborhood	Gene Fusion	Cooccurence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
UBC	ubiquitin C (685 aa)					●				0.965
LEPRE1	leucine proline-enriched proteoglycan (leprecan) 1 (736 aa)						●	●		0.962
HSPB1	heat shock 27kDa protein 1 (205 aa)						●	●		0.955
CRTAP	cartilage associated protein; Necessary for efficient 3-hydroxylation of fibrillar collagen prolyl residues (401 aa)						●	●		0.951
HSP90AA1	heat shock protein 90kDa alpha (cytosolic), class A member 1; Molecular chaperone that promotes the maturation,...						●	●		0.950
PPIB	peptidylprolyl isomerase B (cyclophilin B); PPIases accelerate the folding of proteins. It catalyzes the cis-trans iso...						●	●		0.950
HSPA8	heat shock 70kDa protein 8; Acts as a repressor of transcriptional activation. Inhibits the transcriptional coactivato...						●	●		0.948
HSPH1	heat shock 105kDa/110kDa protein 1; Prevents the aggregation of denatured proteins in cells under severe stress, ...						●	●		0.940
DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1; Interacts with HSP70 and can stimulate its ATPase activity. Stimul...						●	●		0.938
P4HB	prolyl 4-hydroxylase, beta polypeptide; This multifunctional protein catalyzes the formation, breakage and rearrang...					●			●	0.936
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1; Molecular chaperone that promotes the maturation,...						●	●		0.935
EP300	E1A binding protein p300; Functions as histone acetyltransferase and regulates transcription via chromatin remod...						●	●		0.931
CREBBP	CREB binding protein; Acetylates histones, giving a specific tag for transcriptional activation. Also acetylates non-hi...						●	●		0.925
HSPA6	heat shock 70kDa protein 6 (HSP70B'); In cooperation with other chaperones, Hsp70s stabilize preexistent proteins...						●	●		0.924
FKBP4	FK506 binding protein 4, 59kDa; Immunophilin protein with PPIase and co-chaperone activities (By similarity). Com...						●			0.917
KLF13	Kruppel-like factor 13; Represses transcription by binding to the BTE site, a GC-rich DNA element, in competition wi...					●			●	0.911
HSBP1	heat shock factor binding protein 1; Negative regulator of the heat shock response. Negatively affects HSF1 DNA-b...						●			0.909
ENSG00000170276	Heat shock protein beta-2 (182 aa)						●			0.905
UBB	ubiquitin B (229 aa)						●			0.904
DNAJB6	DnaJ (Hsp40) homolog, subfamily B, member 6 (326 aa)						●			0.904

Figure 1. *Protein interactome network of human HSP47 revealing several molecular chaperones as interaction partners for HSP47: This network is produced with the help of STRING 10 (7) with confidence score >0.9. (A) Interactome of collagen-specific chaperone and its assistance in collagen triplet formation. (B) Details of top HSP47-protein interaction partners with their confidence scores. Evidences are marked by a black dot.*

Table 1. *Top protein-protein interaction partners of HSP47.*

Protein	Protein name	Chromosomal Location*	Cytoplasmic band*	Gene ID**	ENSEMBL ID***	Uniprot ID	Protein Length	Gene Synonyms	OMIM****
CREBBP	CREB binding protein	16: 3,725,054-3,880,726	16p13.3	1387	ENSG00000005339	Q92793	2,442	CBP, KAT3A, RSTS, RSTS1	600140
EP300	E1A binding protein p300	22: 41,091,786-41,180,079	22q13.2	2033	ENSG00000100393	Q09472	2,414	p300, KAT3B, RSTS2	602700
CRTAP	Cartilage associated protein	3: 33,113,979-33,147,773	3p22.3	10491	ENSG00000170275	O75718	401	CASP, LEPREL3, OI7, P3H5	605497
DNAJB1	DnaJ (Hsp40) homolog subfamily B member 1	19: 14,514,770-14,529,770	19p13.12	3337	ENSG00000132002	P25685, Q6FHS4	340	HSPF1, Hdj1, Hsp40, RSPH16B, Sis1	604572
DNAJB6	DnaJ (Hsp40) homolog subfamily B member 6:	7: 157,335,381-157,417,439	7q36.3	10049	ENSG00000105993	O75190	326	DJ4, DnaJ, HHDJ1, HSJ-2, HSJ2, LGMD1D, LGMD1E, MRJ, MSJ-1	611332
FKBP	FK506-binding protein 4	6: 35,573,585-35,728,583	6p21.31	2289	ENSG00000096060	Q13451	457	AIG61, FKBP54, P54, PPIase, Ptg-10, FKBP5	602623
HSPA6	Heat shock 70kDa protein 6	1: 161,524,540-161,526,910	1q23.3	3310	ENSG00000173110	P17066	643	HSP70B’	140555
HSPA8	Heat shock 70kDa protein 8	11: 123,057,489-123,063,230	11q24.1	3312	ENSG00000109971	P11142, V9HW22	646	HEL-33, HEL-S-72p, HSC54, HSC70, HSC71, HSP71, HSP73, HSPA10, LAP-1, LAP1, NIP71	600816
HSPB1	heat shock protein beta-1	7: 76,302,544-76,304,295	7q11.23	3315	ENSG00000106211	P04792, V9HW43	205	CMT2F, HEL-S-102, HMN2B, HS.76067, HSP27, HSP28, Hsp25, SRP27	602195
HSPB2	heat shock protein beta-2	11: 111,912,242-111,914,093	11q23.1	3316	ENSG00000170276	Q16082	182	MKBP, HSP27, Hs.78846, LOH11CR1K	602179
HSPH1	Heat shock 105kDa/110kDa protein 1	13: 31,134,974-31,162,388	13q12.3	10808	ENSG00000120694	Q92598	858	HSP105, HSP105A, HSP105B, NY-CO-25	610703

Continued

Protein	Protein name	Chromosomal Location*	Cytoplasmic band*	Gene ID**	ENSEMBL ID***	Uniprot ID	Protein Length	Gene Synonyms	OMIM****
HSBP1	Heat shock factor binding protein 1	16: 83,807,843-83,819,737	16q23.3	3281	ENSG00000230989	O75506	76	NPC-A-13	604553
HSP90AA1	Heat shock protein Hsp 90-alph (cytosolic), class A member 1	14: 102,080,738-102,139,699	14q32.31	3320	ENSG00000080824	P07900	854	EL52, HEL-S-65p, HSP86, HSP89A, HSP90A, HSP90N, HSPC1, HSPCA, HSPCAL1, HSPCAL4, HSPN, Hsp103, Hsp89, Hsp90, LAP-2, LAP2	140571
HSP90AB1	Heat shock protein Hsp 90-alpha (cytosolic), class B member 1	6: 44,246,166-44,253,888	6p21.1	3326	ENSG00000096384	P08238	724	D6S182, HSP84, HSP90B, HSPC2, HSPCB	140572
LEPRE1	Leucine proline-enriched proteoglycan (leprecan) 1	1: 42,746,335-42,767,084	1p34.2	64175	ENSG00000117385	Q32P28	736	GROS1, OI8, P3H1,	610339
KLF13	Kruppel-like factor 13	15: 31,326,855-31,435,665	15q13.3	51621	ENSG00000169926	Q9Y2Y9	288	BTEB3, FKLF2, NSLP1, RFLAT-1, RFLAT1	605328
P4HB	Prolyl 4-hydroxylase beta subunit	17: 81,843,159-81,860,694	17q25.3	5034	ENSG00000185624	P07237	508	CLCRP1, DSI, ERBA2L, GIT, P4Hbeta, PDI, PDIA1, PHDB, PO4DB, PO4HB, PROHB	176790
PIPB	Peptidyl-prolyl isomerase B	15: 64,155,812-64,163,205	15q22.31	5479	ENSG00000166794	P23284	216	B, CYP-S1, CYPB, HEL-S-39, OI9, SCYLP	123841
UBB	Ubiquitin B	17: 16,380,798-16,382,745	17p11.2	7314	ENSG00000170315	P0CG47, Q5U5U6	229	HEL-S-50	191339
UBC	Ubiquitin C	12: 124,911,604-124,917,368	12q24.31	7316	ENSG00000150991	P0CG48	685	HMG20	191340

*Genome assembly: GRCh38.p12 (GCA_000001405.27); **NCBI gene ID; ***Ensembl.

are encoded by the genes- *HSPA6* and *HSPA8*, which are mapped to chromosomal regions 1q23.3 and 11q24.1 in the human genome, respectively (Table 1). These two ubiquitous molecular chaperones (HSPA6 and HSPA8) are members of core Hsp70 machinery and these proteins have critical roles in proper protein folding, protein degradation, protein translocation across membranes, and protein–protein interactions (17). Another interaction partner of HSP47 network is heat shock 105 kDa/110 kDa protein 1 (HSPH1), which also contains HSP70 (PF00012.20) in the region of 3–704 with total protein length 858 (Figure 3I). Gene *HSPH1* mapped on13q12.3 genomic fragment (Table 1), which encodes for HSPH1 protein. The other two very important heat-shock protein 27 (HSP27) homologs include heat shock factor binding protein 1 (HSPB1) and 2 (HSPB2) with size 205 and 182 amino acids with a protein domain HSP20 (PF00011.20) in the region of 88–183 and 70–162, respectively (Figure 3J and K). *HSPB1* gene is localized on human chromosome 7 (7q11.23), while HSPB2 is mapped to 11q23.1 region in chromosome 11 (Table 1). It encodes for an enzyme, which is a member of a heat shock protein family. Under environmental stress, HSPB1 translocates from the cytoplasm to nucleus and helps other protein in error-free folding. *HSPB1* gene is majorly involved in the differentiation of a wide range of cell type. Mutation in this gene leads to Charcot–Marie–Tooth Disease, Axonal, Type 2F, and distal hereditary motor neuropathy, Type IIb diseases. HSPB1 is also involved in major cellular processes, including apoptosis, thermotolerance, protein

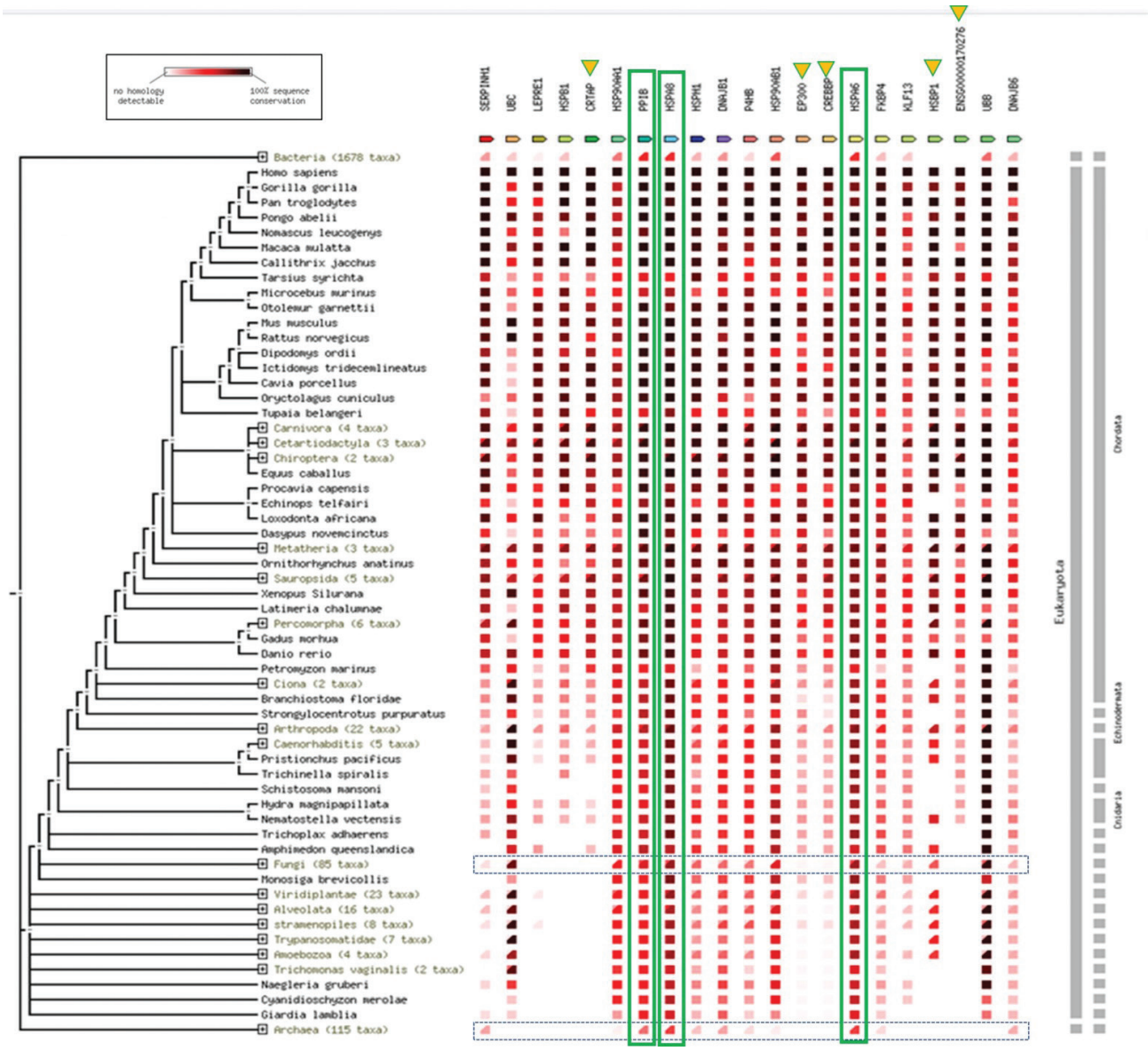


Figure 2. *Origin of protein interactome partners of collagen-chaperone: HSP47 depicts a mixture of interactions originated at different time frames, the couple together with ancient and recently originated proteins: Three proteins are highly conserved from archaea to human (marked in green boxes) and five are missing in fungi (yellow triangle).*

disaggregation, and cell differentiation and development. HSPB2 has a crucial role in binding and activating myotonic dystrophy protein kinase; hence, it is also called as myotonic dystrophy kinase binding protein (MKBP). This protein HSPB1/MKBP is a major player in maintenances of muscle structure and function (18). HSP27 has a highly conserved α-crystallin domain that is enriched with β-sheet structures. Small heat shock proteins (sHSPs) bind to aggregated proteins in ATP-independent manner and which are subsequently tackled by either by HSP70 system (Hsp70 plus Hsp40 system) or Hsp70/104 bichaperone (19) system for protein disaggregation. Disaggregated proteins either get refolded back into native proteins or degraded by autophagy and/or proteasomal system. In addition, HSP27 recently was reported to be involved in cancer-related retinopathy, suggesting its role in developing cancer therapeutics (20). *HSBP1* gene is localized in the genomic fragment of 16q23.3 on the chromosome 16 (Table 1), encodes for HSBP1 protein, which is 76 amino acids long with HSBP1 (PF06825.12) domain in the region of 10–60 (Figure 3L). HSBP1 is a member of the sHSPs family and this protein prevents the aggregation of denatured and stress-induced misfolded proteins (21). There are two HSP90 homologs acting as protein–protein interaction partners: HSP90AA1 (or Hsp90α) and HSP90AB1 (Hsp90β), belong to HSP90 family, which is a well-characterized, well-documented conserved and critical eukaryotic chaperone family (22). These homologs *HSP90AA1* and *HSP90AB1* are mapped into the human chromosomes 14 (14q32.31) and 6 (6p21.1), respectively (Table 1). These two proteins have two types of protein domains, such as HATPase_C (PF02518.25) and HSP90 (PF00183.17) in the N-terminal and the C-terminal end (Figure 3M and N). HSP90 proteins are required for the proper function of other chaperones. These HSP90 proteins are essential for the maturation, structural maintenance and protein folding, intracellular trafficking, and other signal transduction events (22,23). HSP90AB1 was shown to be overexpressed during cancer, which prevents misfolding, and degradation of both mutated (for example Ras and p53) and over-expressed oncoproteins (for example p53 and Her2) (24). Leucine proline-enriched proteoglycan 1 (*LEPRE1*, leprecan) gene is located on the human chromosome1 (cytoplasmic location 1p34.2) (Table 1). LEPRE1 encodes prolyl 3-hydroxylase 1 (P3H1), which is a member of collagen prolyl hydroxylase family with 736 amino acid long and it possesses a single domain of 96 residues long as OG-Fe(II) oxygenase superfamily (2OG-FeII_Oxy_3, PF13640.5) in the region of 584–661 (Figure 3O). Peptidyl-prolyl isomerase B (PPIB)/CyPB plays an instrumental role in the formation of the collagen prolyl 3-hydroxylation complex with P3H1 and CRTAP in the ER (11).The activity required for proper collagen synthesis and assembly (11). Mutation in this gene is associated with OI type VIII.

Kruppel-like factor 13 (KLF13) protein is encoded by *KLF13* gene is localized on human chromosome 15 (Table 1) and KLF13 protein is 288 amino acids long with three copies of Zf-C2H2 (PF00096.25) domain from mid to the C-terminal end (Figure 3P). It is a member of KLFs family of Cys2-His2 (C2H2) zinc-finger transcription factors and it has play function in a myriad of physiological roles during cell differentiation and development processes (25). *P4HB* gene is localized on human chromosome 17 (cytoplasmic ban 17q25.3), which encodes for prolyl 4-hydroxylase beta subunit (P4HB) protein of size 508 amino acids with three protein domains made of two thioredoxin (PF00085.19) in the N-terminal (25–131 residues) and the C-terminal ends (368–472 residues) and one thioredoxin_6 (PF13848.5) in the middle located in 161–345 residues (Figure 3Q). This protein is a member of the disulfide isomerase family and it is also called protein disulfide isomerase (PDI). P4HB/PDI is the ubiquitously expressed protein which helps in the correction of disulfide bridges in nascent polypeptide chains (26). Hence, P4HB/PDI plays an instrumental role in the protein folding and the cellular concentration of this protein is critical for protein aggregation/disaggregation (26). Mutations in this protein are involved in a new form of OI-like disorder, known as Cole-Carpenter syndrome (26). *PPIB* gene is located on human chromosome 15 (cytoplasmic band 15q22.31), which encodes for PPIB of size 216 residues with pro-isomerase (PF00160) domain in the region of 47–204 residues (Figure 3R) and it is also known as cyclophilin B (CyPB). PPIB/CyPB plays an instrumental role in the formation of the collagen prolyl 3-hydroxylation complex with P3H1 and CRTAP in the ER (11). Mutational variation in this gene leads to recessive forms of OI. The PPIases enzyme helps in the catalysis process of the cis-trans isomerization of proline imidic peptide bonds in proteins and it ultimately assists in protein folding and provides structural stability (11). PPIB is a member of peptidyl-prolyl cis-trans isomerase (PPIase) with a β-barrel structure like cyclophilin and is localized inside the ER lumen (27). Due to its localization to this specialized cellular compartment, it is involved in many biological processes, such as post-translational modification and proper folding of proteins, such as type I collagen (28).

Finally, there are two ubiquitin proteins, which exists as interaction partner of HSP47: ubiquitin B (UBB) and ubiquitin C. These proteins are variable in protein length with 229 and 685 amino acids and similarly these two possess three and nine ubiquitin domains (72 amino acids each; PF00240.22), respectively (Figure 3S and T). UBB and UBC are encoded by *UBB* and *UBC* genes mapped on chromosomes 17 (17p11.2) and 12 (12q24.31), respectively (Table 1). They are highly conserved eukaryotic proteins involved in protein ubiquitination, which is a multifaceted dynamic post-translational change occurring with help of the ubiquitin code present in the 72 amino acids of ubiquitin domain (29) with Pfam ID—PF00240.22. The protein ubiquitination results in clearance of aberrant proteins for their possible degradation by the proteasome and hence, this process is associated with various physiological cycles and in

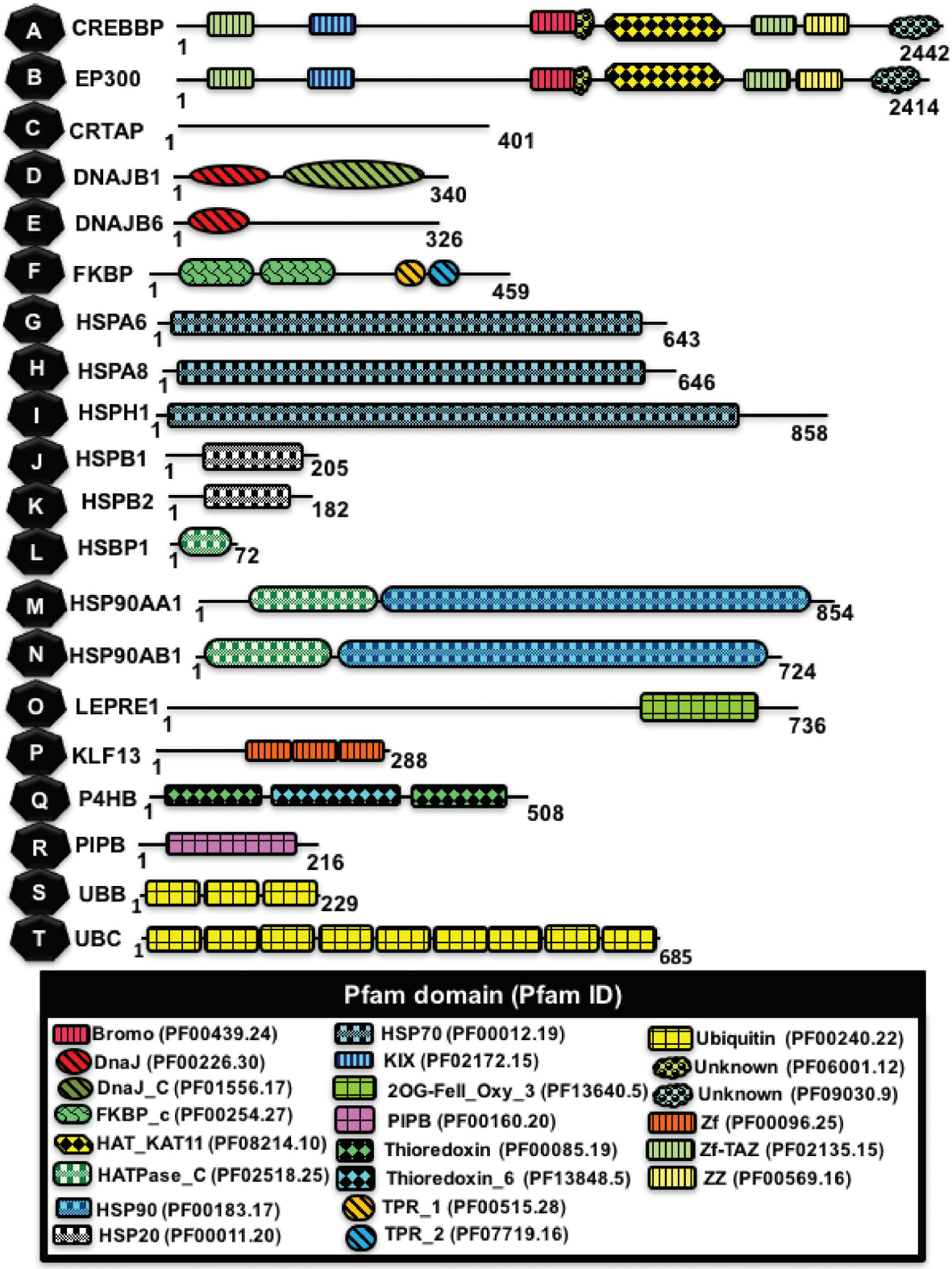


Figure 3. *Overview of protein domain architecture of top 20 proteins interacting with HSP47: Pfam protein domains and corresponding Pfam IDs are listed in the box: (A) CREBBP—CREB binding protein; (B) EP300—E1A binding protein p300; (C) CRTAP—Cartilage associated protein; (D) DNAJB1—DnaJ (Hsp40) homolog subfamily B member 1; (E) DNAJB6—DnaJ (Hsp40) homolog subfamily B member 6; (F) FKBP—FK506-binding protein 4; (G) HSPA6—Heat shock 70 kDa protein 6; (H) HSPA8—Heat shock 70 kDa protein 8; (I) HSPH1—Heat shock 105 kDa/110 kDa protein 1; (J) HSPB1—heat shock protein beta-1; (K) HSPB2—heat shock protein beta-2; (L) HSBP1—heat shock factor binding protein 1; (M) HSP90AA1—heat shock protein Hsp 90-alph(cytosolic), class A member 1; (N) HSP90AB1—heat shock protein Hsp 90-alpha (cytosolic), class B member 1; (O) LEPRE1—Leucine proline-enriched proteoglycan (leprecan) 1; (P) KLF13—Kruppel-like factor 13; (Q) P4HB—Prolyl 4-hydroxylase beta subunit; (R) PIPB—Peptidyl-prolyl isomerase B; (S) UBB—Ubiquitin B; (T) UBC—Ubiquitin C.*

regulations of various signaling pathways (29). Mutations in these two ubiquitins are related to different human diseases, including Huntington's disease, Alzheimer's disease, and polyglutamine disease (30). The findings of the study are coinciding with other interactome analyses that chaperones interact with each other in the large interactome, also called as chaperome (31). Previously, it is known that and CRTAP HSP47, P3H1, and PPIB/CyPB plays an instrumental role in the formation of the collagen prolyl 3-hydroxylation complex in the ER (11). Several of HSP47 interaction partners also are markers of the panel of osteogenesis imperfecta (Version 1.12) under Rare Disease 100 K (*https://panelapp.genomicsengland.co.uk/panels/196/)*. Taken together, the protein–protein network of HSP47 reported in the current study is a critical protein network in collagen-related disorders. Hence, remaining members of interactions partners must be taken into consideration for future evaluations. Expression of HSP47 in different cancers tissues and normal tissues

It is also important to know, the expression pattern of HSP47 in different cancer types. To evaluate expression patterns of HSP47, the study team extracted data from the database of differential expression of the protein in cancer, dbDEPC 3.0 (8). In 11 types of cancer, HSP47 was found to be up-regulated among four cancers types based on the number of experiments. The cancer types included meningioma, colorectal cancer, hepatocellular carcinoma, and breast cancer (Figure 4; Table 2). HSP47

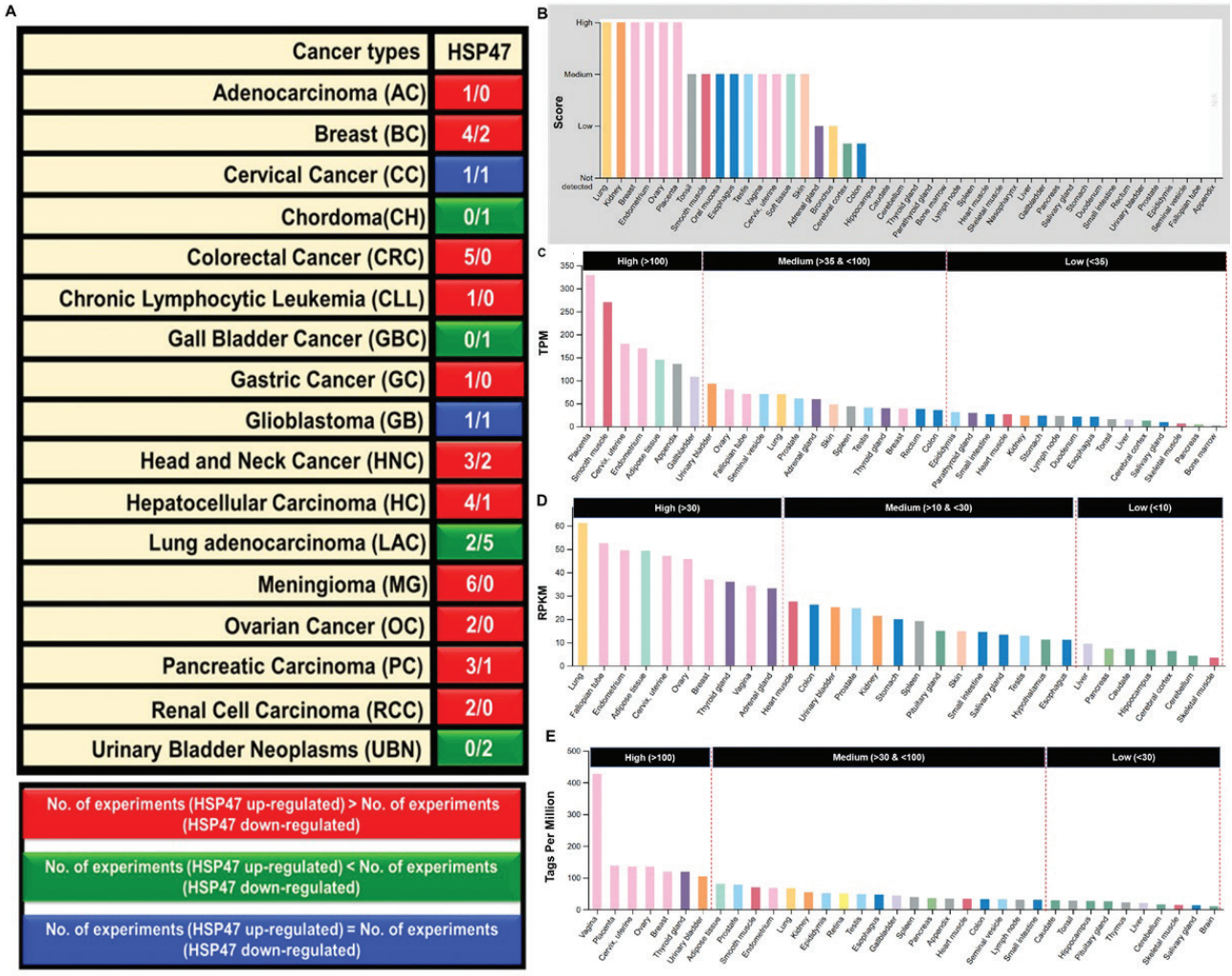


Figure 4. *Overview of different expression patterns of human HSP47 in cancer and different normal tissue types: (A) Summary of HSP47 expression pattern in different cancer types. This expression pattern was deduced from dbDEPC 3.0 (8). (B) Summary of human HSP47 protein expression patterns in different normal tissues derived from HPA (https://www.proteinatlas.org/). (C) Overview of human HSP47 expression patterns using RNA-Seq data from HPA and expression values depicted as mean TPM, corresponding to mean values of the different individual samples from each tissue types. (D) Summary of RNA-seq based HSP47 expression patterns in different normal tissues and the values are shown as median reads per kilobase per million mapped reads (RPKM), derived from the GTEx (https://gtexportal.org) datasets. (E) Overview of the expression pattern of HSP47 in normal human tissues reported as tags per million extracted through cap analysis of gene expression (CAGE) in the FANTOM5 project data (http://fantom.gsc.riken.jp/5/). Similar functional tissue groups are color coded with same colors in B–E.*

Table 2. *Overview of differential expression patterns of HSP47 in different cancer types.*

dbDEPC ID	Regulation Change	Ratio	Cancer type* (Sample type**)	Study	Experimental design		Pubmed ID
					Sample control	Sample case	
EXP00661	Up	7.54	AC (TI)	Normal vs. Cancer	adjacent nonmalignant tissue vessels	invasive ductal carcinoma vessels	21401208
EXP00211	Up	1.9	BC (TI)	Treatment (tamoxifen-sensitive vs. tamoxifen-resistant)	tumors were sensitive to tamoxifen therapy	tumors were resistant to therapy	19329653
EXP00230	Up	1.6	BC (CL)	Normal vs. Cancer	normal MCF10A1	low grade MCF10CA1h	20543960
EXP00695	Up	0.59	BC (CL)	Treatment (none vs. adriamycin-resistant)	MCF-7 breast cancer cells	adriamycin-resistant breast cancer MCF-7/ADR cells	23214712
EXP00203	Down	0.07	BC (CL)	Metastasis	precancerous (MCF10AT1)	malignant, metastatic cellular phenotype (MCF10CA1a)	18729497
EXP00410	Down	-2.08	BC (TI)	Treatment (drug-sensitive vs.drug-resistant)	drug sensitive breast cancer tissues	drug resistant breast cancer tissues	22074005
EXP00095	Up		BC (TI)	Metastasis	Tumors That Have Not Metastasized to the Lymph Nodes	Tumors That Have Metastasized to the Lymph Nodes	18257521
EXP00386	Down	0.58	CC (CL)	Treatment (none *vs*. Zey-treated)	HeLa cells	HeLa cells treated with Zey	26130516
EXP00621	Up		CC (CL)	Treatment (none *vs*. 6-Shogaol-treated)	human cervical cancer HeLa cells	HeLa cells treated with 6-Shogaol	23243437
EXP00624	Down	0.6	CH (TI)	Cancer *vs*. Cancer	endophytic type (Type I) tissue samples	exophytic type (Type II) tissue samples	25793716
EXP00707	Up	9.78	CRC (TI)	Normal *vs*. Cancer	adjacent normal tissues	CRC tumor tissues	26054784
EXP00363	Up	1.84	CRC (TI)	Normal *vs*. Cancer	noncancerous colonic epithelial tissue	CRC tissue	24381081
EXP00533	Up	1.74	CRC (TI)	Normal *vs*. Cancer	adjacent normal mucosa	CRC tumour tissue	21808808
EXP00399	Up		CRC (TI)	Normal *vs*. Cancer	healthy colorectal tissue	colorectal cancer tissue samples	25247386
EXP00517	Up		CRC (TI)	Normal *vs*. Cancer	their matched normal tissues	colorectal cancer tissues	22154799
EXP00731	Down		GBC (CL)	Metastasis	non-invasive gallbladder cancer cell lines	highly invasive gallbladder cancer cell lines	26530123
EXP00725	Up		GC (TI)	Normal *vs*. Cancer	adjacent normal gastric tissues	gastric cancer tissues	26398045
EXP00670	Up	3.88	GB (TI)	Normal *vs*. Cancer	pooled tissue from control subjects	pooled tissue from GBM patients	22219345

Continued

dbDEPC ID	Regulation Change	Ratio	Cancer type* (Sample type**)	Study	Experimental design Sample control	Sample case	Pubmed ID
EXP00609	Down	0.06	GB (CL)	Cancer *vs*. Cancer	CD90- cells (which do not exhibit stem-like properties)	CD90+ stem-like cells from glioblastoma multiforme tissue sections	23436586
EXP00404	Up		LC (TI)	Normal *vs*. Cancer	adjacent non-cancerous tissue	laryngeal cancer tissues	25874882
EXP00387	Up	1.46	NC (TI)	Normal *vs*. Cancer	adjacent non-tumor tissues	NPC tissues	25648846
EXP00467	Down		NC (CL)	Normal *vs*. Cancer	nasopharyngeal epithelial cells (NP69 and NP460)	NPC C666-1 cells	25857718
EXP00066	Up	9.1	OC (TI)	Normal *vs*. Cancer	adjacent non-tumorous tissues	primary oral squamous cell carcinoma (OSCC) lesions	19297561
EXP00422	Down		OC (TI)	Normal *vs*. Cancer	adjacent normal tissues	OSCC-derived cancer tissue samples	26159854
EXP00730	Up	2.32	HC (TI)	Normal *vs*. Cancer	non-HCC tissue	HCC tissues	22082227
EXP00145	Up	1.9	HC (CL)	Metastasis	MHCC97L (low metastatic potential) cell line	HCCLM6 (high metastatic potential) cell line	19016532
EXP00465	Down		HC (CL)	Normal *vs*. Cancer	normal liver cells (human Chang liver cells)	highly metastatic HCC (MHCC97-H) cells	21423987
EXP00631	Up		HC (TI)	Normal *vs*. Cancer	late-recurrent (LR)-HCC tissues and adjacent nontumor tissues	early-recurrent (ER)-HCC tissues	24967658
EXP00776	Up		HC (TI)	Normal *vs*. Cancer	normal liver tissues(NL)	HBV-related HCC liver tissues(HCC)	26883192
EXP00625	Up	1.6	CLL (CL)	Cancer *vs*. Cancer	mutated chronic lymphocytic leukemia (M-CLL) cells	unmutated chronic lymphocytic leukemia (UM-CLL) cells	25645933
EXP00438	Up	4.33	LAC (TI)	Normal *vs*. Cancer	Normal bronchial epithelium (NBE) tissues	Lung squamous cell carcinoma tissues	23977169
EXP00650	Up	3	LAC (TI)	Normal *vs*. Cancer	normal bronchial epithelium tissues	human lung squamous tissues carcinoma	22500095
EXP00510	Down	0.3	LAC (TI)	Normal *vs*. Cancer	atypical hyperplasia or carcinoma in situ tissues	invasive LSCC tissues	22298307

Continued

dbDEPC ID	Regulation Change	Ratio	Cancer type* (Sample type**)	Study	Experimental design		Pubmed ID
					Sample control	Sample case	
EXP00508	Down	0.23	LAC (TI)	Normal *vs*. Cancer	normal bronchial epithelium tissues	invasive LSCC tissues	22298307
EXP00509	Down	0.23	LAC (TI)	Normal *vs*. Cancer	squamous metaplasia tissues	invasive LSCC tissues	22298307
EXP00601	Down		LAC (CL)	Treatment (none *vs*. G6PD-knockdown)	lung cancer line A549	A549 cells with G6PD knockdown	23742107
EXP00498	Down		NSCLC (CL)	Treatment (miRNA mimic-treated *vs*. miR-control-treated)	highly metastatic human lung-cancer cell line SPC-A-1sci transfected with the miR-control	SPC-A-1sci cells transfected with the miRNA mimic	25833338
EXP00782	Up		MG (TI)	Normal *vs*. Cancer	samples collected from normal brain tissues	grade MGI tissue specimens collected from patients radiologically suspected with MGs	25413884
EXP00783	Up		MG (TI)	Normal *vs*. Cancer	samples collected from normal brain tissues	grade MGII tissue specimens collected from patients radiologically suspected with MGs	25413884
EXP00784	Up		MG (TI)	Normal *vs*. Cancer	samples collected from normal brain tissues	grade MGIII tissue specimens collected from patients radiologically suspected with MGs	25413884
EXP00785	Up		MG (TI)	Normal *vs*. Cancer	samples collected from normal brain tissues	grade MGI tissue specimens collected from patients radiologically suspected with MGs	25413884
EXP00786	Up		MG (TI)	Normal *vs*. Cancer	samples collected from normal brain tissues	grade MGII tissue specimens collected from patients radiologically suspected with MGs	25413884
EXP00787	Up		MG (TI)	Normal *vs*. Cancer	samples collected from normal brain tissues	grade MGIII tissue specimens collected from patients radiologically suspected with MGs	25413884

Continued

dbDEPC ID	Regulation Change	Ratio	Cancer type* (Sample type**)	Study	Experimental design		Pubmed ID
					Sample control	Sample case	
EXP00507	Up	1.82	OVC (TI)	Normal *vs*. Cancer	normal ovarian epithelial tissues	ovarian cancer tissues	22807371
EXP00477	Up		OVC (CL)	Treatment (cisplatin-sensitive *vs*. cisplatin-resistant)	ovarian cancer cell line A2780	cisplatin-resistant ovarian cancer cell line A2780-DR	25096996
EXP00298	Up	2	PC (TI)	Normal *vs*. Cancer	adjacent healthy tissue from patients	Samples of pancreatic adenocarcinomas from patients	15526344
EXP00298	Down	0.2	PC (TI)	Normal *vs*. Cancer	adjacent healthy tissue from patients	Samples of pancreatic adenocarcinomas from patients	15526344
EXP00497	Up		PC (TI)	Normal *vs*. Cancer	low-grade PAC tissues and adjacent nontumor tissues	high grade pancreatic adenocarcinoma tissues	23851313
EXP00453	Up		PDAC (CL)	Normal *vs*. Cancer	CD24(-) cells dissected from patient-matched adjacent normal tissues.	CD24(+) adenocarcinoma cells from early stage tumors	23679566
EXP00765	Up	1.89	RCC (TI)	Normal *vs*. Cancer	adjacent normal renal tissues	tissue samples from primary RCC lesions	24548857
EXP00269	Up		RCC (TI)	Normal *vs*. Cancer	normal tissues	clear cell renal cell carcinoma (ccRCC) tissues, Grading 1-4	19164279
EXP00558	Down	0.41	UBN (CL)	Cancer *vs*. Cancer	highly invasive (T24) bladder cancer cells	highly metastatic (T24T) bladder cancer cells	23308193
EXP00579	Down	0.17	UBN (CL)	Normal *vs*. Cancer	normal bladder epithelial HCV29 cell lines	metastatic bladder cancer cell lines YTS1	26230496

*Cancer type -- AC - Adenocarcinoma; BC - Breast Cancer; CC- Cervical Cancer; CH - Chordoma; CRC - Colorectal Cancer; GBC - Gall Bladder Cancer; GC - Gastric Cancer; GB - Glioblastoma; LC - Laryngeal cancer; NC - Nasopharyngeal carcinoma; OC - Oral Cancer; HC - Hepatocellular Carcinoma; CLL - Chronic Lymphocytic Leukemia; LAC - Lung Adenocarcinoma; NSCLC - Non-small Cell Lung Carcinoma; MC - Meningioma; OVC - Ovarian Cancer; PC - Pancreatic Carcinoma; PDAC - Pancreatic Ductal Adenocarcinoma; RCC - Renal Cell Carcinoma; UBN - Urinary Bladder Neoplasms

**Sample type -- CL - cell line; TI - tissue

was found to be down-regulated in chordoma, lung adenocarcinoma, and urinary bladder neoplasms (Figure 4; Table 2). These inferences made us further investigate that how the expression patterns of HSP47 are in different normal human tissues. To evaluate expression pattern, the study group scanned three large resources of human gene expression datasets as HPA (https://www.proteinatlas.org/), GTEx (https://gtexportal.org), and FANTOM5 project (http://fantom.gsc.riken.jp/5/). Upon evaluating protein level expression of HPS47 using the HPA resource, it was found that human HSP47 protein is highly expressed in the normal tissues of lung, kidney, breast, endometrium, ovary, and placenta (Figure 4B), whereas expression of HPS47 was found as medium

levels in tissues of tonsil, smooth muscle, oral mucosa, esophagus, testis, vagina, cervix (uterine), soft tissue, and skin (Figure 4B). Low level of expression of HSP47 was found in tissues of the adrenal gland, bronchus, cerebral cortex, and colon (Figure 4B). Furthermore, the current study also examined Ribonucleic acid sequence (RNA-Seq) data for HSP47 from the HPA resource. Placenta tissues had the highest expression of RNA seq levels with 329.1 transcripts per million (TPM), whereas other normal tissues with higher level of expression pattern (>100 TPM) included smooth muscle (270.5 TPM), cervix, (uterine, 179.6 TPM), endometrium (169.8 TPM), adipose tissue (145.4 TPM), appendix (135.9 TPM), and gallbladder (108.8 TPM). Fourteen tissues had medium levels of HSP47 expression (<100 and >35 TPM) with top two being urinary bladder (93 TPM) and ovary (80.6 TPM) and the last two being rectal (38 TPM) and colon tissues (35.4 TPM). Sixteen tissues had low levels of HSP47 expression (<35 TPM) with top two being epididymis (31.1 TPM) and parathyroid gland (29 TPM) and the last two being pancreas (four TPM) and bone tissues (2.2 TPM). Using FANFOM5 dataset, the study found that HSP47 to be highly expressed (>100 tags per millions) among normal tissues, including vagina, placenta, cervix (uterine), ovary, breast, thyroid gland, and urinary bladder (Figure 4E). The study also found medium (>100 tags per millions) and lower levels of HSP47 expression in 19 and 10 tissues types, respectively (Figure 4E).

Conclusion

Overall, the study was successful in finding HSP47 expression patterns among several normal tissues using three different publicly available datasets. It also assessed the expression pattern of HSP47 in human cancer types. These findings will encourage further studies focusing on the role of HSP47 in human diseases, along with our recent study of pathogenic mutational hotspot profilings of HSP47 (32).

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Consent for publication
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