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MINI REVIEW

Diversity in heat shock protein families: functional implications in virus infection with a comprehensive insight of their role in the HIV-1 life cycle

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Abstract

Heat shock proteins (HSPs) are a group of cellular proteins that are induced during stress conditions such as heat stress, cold shock, UV irradiation and even pathogenic insult. They are classified into families based on molecular size like HSP27, 40, 70 and 90 etc, and many of them act as cellular chaperones that regulate protein folding and determine the fate of mis-folded or unfolded proteins. Studies have also shown multiple other functions of these proteins such as in cell signalling, transcription and immune response. Deregulation of these proteins leads to devastating consequences, such as cancer, Alzheimer's disease and other life threatening diseases suggesting their potential importance in life processes. HSPs exist in multiple isoforms, and their biochemical and functional characterization still remains a subject of active investigation. In case of viral infections, several HSP isoforms have been documented to play important roles with few showing pro-viral activity whereas others seem to have an anti-viral role. Earlier studies have demonstrated that HSP40 plays a pro-viral role whereas HSP70 inhibits HIV-1 replication; however, clear isoform-specific functional roles remain to be established. A detailed functional characterization of all the HSP isoforms will uncover their role in cellular homeostasis and also may highlight some of them as potential targets for therapeutic strategies against various viral infections. In this review, we have tried to comprehend the details about cellular HSPs and their isoforms, their role in cellular physiology and their isoform-specific functions in case of virus infection with a specific focus on HIV-1 biology.

Keywords : HSP · Virus · Antiviral · HIV-1 · HSP isoforms · Chaperones · HSP27 · HSP40 · HSP60 · HSP70 · HSP90 · HSP110

Introduction

Heat shock proteins (HSPs) are one of the most evolutionarily conserved groups of cellular proteins found across almost all the living organisms. In humans, these proteins are known to be modulated upon stress conditions such as heat stress, cold shock, ultraviolet (UV) irradiation, exposure to heavy metals and microbial infection. The stress signal is usually a flux of non-native proteins that triggers the activation of heat shock factors (HSF), which in turn results in the change in expression of HSPs (Pirkkala et al. 2001) (Fig. 1). HSPs, also referred to as molecular chaperones, have been well characterized for their roles in housekeeping functions such as protein folding, assembly, transport and degradation (Georgopoulos and Welch 1993; Parsell et al. 1993; Becker and Craig 1994). However, studies have later shown multiple other functions of these proteins such as in cell signalling pathways, transcription regulation and immune response. Mammalian HSPs have been initially classified into different groups based on their molecular weight such as small heat shock proteins, HSP40, HSP70, HSP90, HSP100 and chaperonins (Csermely et al. 1998). However, in 2009, they were renamed as HSPB, DNAJ, HSPA, HSPC, HSPH and chaperonin/CCT/HPD, respectively (Kampinga et al. 2009). Interestingly, each family of cellular HSPs are now known to comprise several members or isoforms as listed in Table 1. The number varies vastly from one family to the other as highlighted in the table. The main function of many of these isoforms is yet to be characterized, although they seem to be highly conserved across different species and various homologues are found in even some of the most primitive organisms such as archaea, bacteria and fungi (Feder and Hofmann 1999; Large et al. 2009). Heat

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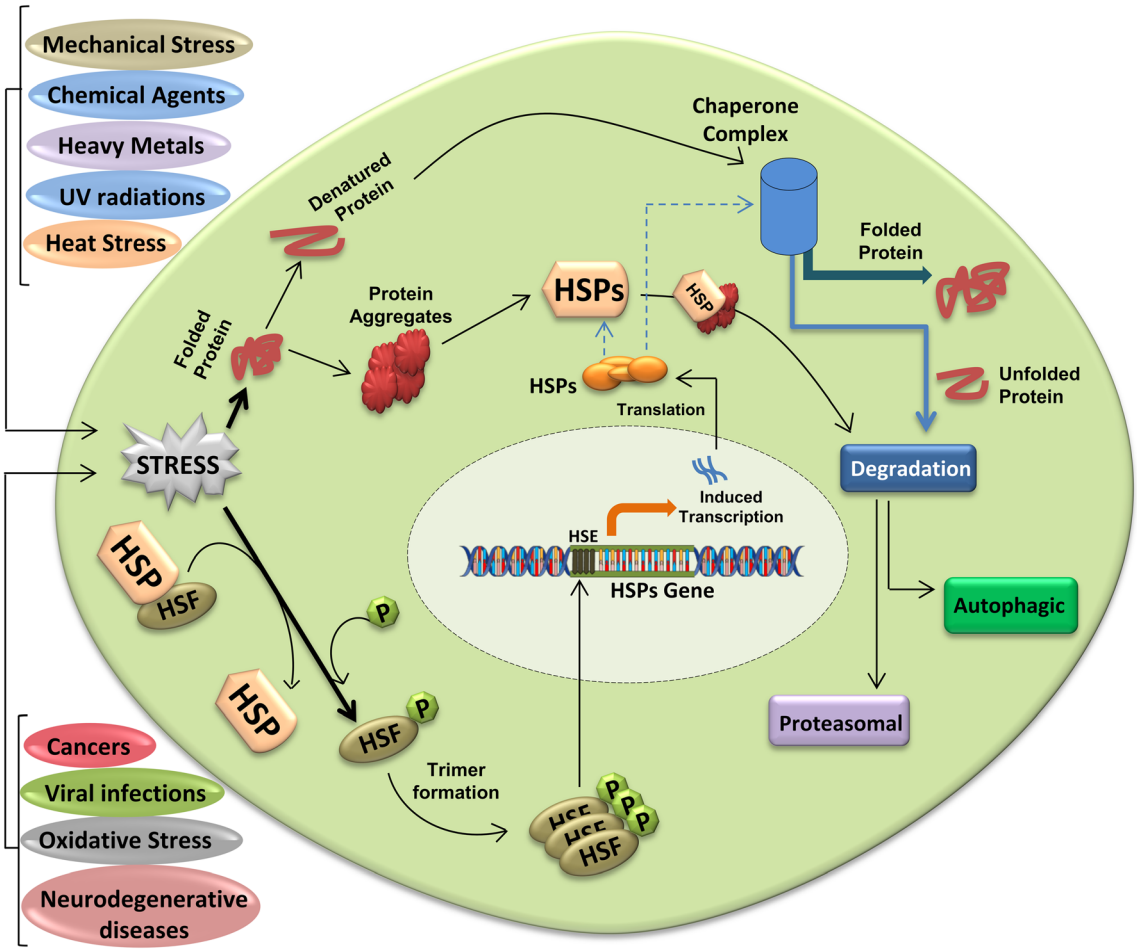

Fig. 1 Molecular events and biological functions of different HSPs to maintain cellular homeostasis during stress conditions. Various kinds of stress elements induce denaturation of cellular proteins or formation of protein aggregates followed by transcription of different HSPs through activation of heat shock factors (HSFs). These HSPs form chaperone complex and refold the denatured proteins into the folded form or bind with protein aggregates/unfolded proteins and clear them through proteasomal or autophagic degradation.

shock proteins were first discovered in the fruit fly *Drosophila melanogaster* chromosomal puffs, when they were placed in temperatures above 36 °C (Ritossa 1962). Since then, heat shock proteins have been extensively investigated for their role in several biological process such as apoptosis (Takayama et al. 2003), neuro-degeneration and aging (Leak 2014), development (Miller and Fort 2018) and immunomodulation (Zininga et al. 2018), in addition to their chaperone function.

Intensive exploration of HSPs and their role in the past few decades have highlighted them as potential therapeutic targets not only for various diseases including cancer and autoimmune conditions but also for viral infections. For example, the adenoviral E1A gene induces the 70-kDa heat-inducible HSP70 gene expression in HeLa cells (Nevins 1982). Many reports have shown HSP modulation during herpes simplex virus (HSV) infection. A latent infection of HSV type 2 causes an increase in the 90-kDa, 70-kDa and 72-kDa cellular heat stress proteins in human neuroblastoma cells (Yura et al. 1987). Both HSV-1 and HSV-2 infection in mouse L cells causes an increase in the HSP70 mRNA levels within 4 h post infection (Kobayashi et al. 1994). EBV (Epstein-Barr virus) infection of human B lymphocytes induces HSP70 and HSP90 at the mRNA and protein levels which is dependent on the EBV-induced trans-membrane Ca^{2+} currents (Cheung and Dosch 1993). Modulation of HSPs has been observed during RNA virus infections as well. HSP70 associates with the capsid precursor P1 of poliovirus type 1 and coxsackievirus B1 (Macejak and Sarnow 1992). Studies have shown that HSP70 was expressed on the cell surface of the HTLV-1-transformed cells. Human immunodeficiency virus (HIV), another well-known retrovirus, causes an increase in HSP70 in chronically infected lymphoma cells (Di Cesare et al. 1992) and lymphocytes from HIV-infected patients (Agnew et al. 2003). There is also an increase in the levels of HSP40 (Kumar and Mitra 2005; Solis et al. 2006).

Although a number of reviews are available regarding the role of HSPs in various physiological processes and disease conditions including pathogenic insults with viral infections, due to lack of availability in literature related to the function of

Table 1 Isoforms of different heat shock protein families, their alias, cellular and sub-cellular location, length and mass

Gene name	Other names	Cellular location	Subcellular location	Length (a.a.)	Mass (kDa)
sHSPs/HSPB					
HSPB1	HSP27, HSP28,	Intracellular	Plasma membrane, cytosol	205	23
HSPB2	MXBP, HSP27, DMPK-binding protein, Hs.78846	Intracellular	Not known	182	20
HSPB3	HSPL27, HSP 17, HSP27, DHMN2C	Intracellular	Nuclear speckles	150	17
HSPB4	Crystallin alpha A, CRYA1, CRYAA	Intracellular	Cytosol and additionally in nucleoplasm	173	20
HSPB5	Crystallin alpha B, CRYA2, CRYAB	Intracellular, Membrane	Plasma member, cytosol	175	20
HSPB6	PPP1R91, FLJ32389, HSP20	Intracellular	Cytosol and additionally in nucleoli, Golgi apparatus	160	17
HSPB7	CvHSP	Intracellular	Nucleoplasm	170	19
HSPB8	CRYAC, E2IG1, HSP22, PP1629, CMT2L	Intracellular	Cytosol and additionally in nucleoplasm, nuclear bodies	196	22
HSPB9	CT51	Intracellular	Not known	159	17
HSPB10	ODF1, CT133, ODF27, ODFPG, ODFP	Intracellular	Not known	250	28
HSPB11	IFT25, PP25, C1orf41, HSPCO34	Intracellular	Nucleoplasm and additionally in cytosol	144	16
HSP40/DNAJ					
DNAJA1	dj-2, hdj-2, HSJ2, HSPF4, NEDD7	Intracellular	Cytosol and additionally in microtubules	397	44.9
DNAJA2	CPR3, DNAJ, DNJ3, HIRIP4	Intracellular	Nucleoli, cytosol and additionally in intermediate filaments	412	45.7
DNAJA3	hTid-1, TID1	Intracellular	Mitochondria and additionally in vesicles	480	52.5
DNAJA4	PRO1472	Intracellular	Plasma membrane, cytosol	397	44.8
DNAJB1	Hsp40, HSPF1, RSPH16B, Sis1,Hdj1	Intracellular	Nucleoplasm	340	38.0
DNAJB2	CMT2T, HSJ1, HSPF3	Intracellular	Nuclear membrane	324	35.6
DNAJB3	HCG3	Not known	Not known	145	15.6
DNAJB4	HLJ1	Intracellular	Nucleoplasm and additionally in plasma membrane, cytosol	337	37.8
DNAJB5	Hsc40	Intracellular	Nucleoplasm and additionally in cytosol	348	39.1
DNAJB6	LGMD1D, MRJ	Intracellular	Nucleoplasm and additionally in cytosol	326	36.1
DNAJB7	HSC3	Intracellular	Not known	309	35.4
DNAJB8	CT156, MGC33884	Intracellular	Cytosol and nucleus	232	25.7
DNAJB9	MDG1	Intracellular	Endoplasmic reticulum, cytosol	223	25.5
DNAJB11	EDJ, ERdj3, HEDJ	Intracellular	Endoplasmic reticulum	358	40.5
DNAJB12	DJ10, FLJ20027	Membrane	Endoplasmic reticulum and additionally in nuclear membrane	409	45.5
DNAJB13	RSPH16A, TSARG6	Intracellular	Plasma membrane	316	36.1
DNAJB14	FLJ14281	Intracellular	Endoplasmic reticulum and nuclear membrane	379	42.5
DNAJC1	DNAJL1, ERdj1, MTJ1	Membrane		554	63.9

Table 1 (continued)

Gene name	Other names	Cellular location	Subcellular location	Length (a.a.)	Mass (kDa)
			Endoplasmic reticulum and nuclear membrane		
DNAJC2	MPHOSPH11, MPP11, ZRF1, ZUO1, zuotin	Intracellular	Cytosol and nucleus	621	72.0
DNAJC3	ERdj6, HP58, P58, P58IPK, PRKRI	Intracellular	Endoplasmic reticulum	504	57.6
DNAJC4	HSPF2, MCG18	Intracellular	Membrane	249	28.2
DNAJC5	CLN4, DNAJC5A, FLJ00118, FLJ13070	Membrane	Golgi apparatus, plasma membrane and additionally in vesicles	198	22.1
DNAJC5B	CSP-beta, MGC26226	Intracellular	Membrane	199	22.5
DNAJC5G	CSP-gamma, FLJ40417	Membrane	Membrane	189	21.4
DNAJC6	KIAA0473, PARK19	Intracellular	Cytosol and additionally in nucleoplasm, plasma membrane	970	105.7
DNAJC7	TPR2, TTC2	Intracellular	Nucleoplasm and additionally in cytosol	494	56.4
DNAJC8	SPF31	Intracellular	Nucleoplasm	253	29.8
DNAJC9	JDD1, SB73	Intracellular	Nucleoplasm and additionally in plasma membrane	260	29.9
DNAJC10	ERdj5, PDIA19	Membrane	Endoplasmic reticulum	793	91.1
DNAJC11	FLJ10737	Intracellular	Mitochondrial	559	63.3
DNAJC12	JDP1	Intracellular	Cytosol	198	23.4
DNAJC13	KIAA0678, RME8	Membrane	Vesicles and additionally in cytosol	2243	254.4
DNAJC14	DNAJ, DRIP78, FLJ32792, HDJ3, LIP6	Intracellular	Endoplasmic reticulum membrane	702	78.6
DNAJC15	DNAJD1, MCJ	Membrane	Mitochondrial membrane	150	16.4
DNAJC16	KIAA0962	Membrane	Vesicles	782	90.6
DNAJC17	FLJ10634	Intracellular	Nucleoplasm	304	34.7
DNAJC18	MGC29463	Intracellular	Cell Junctions and additionally in cytosol	358	41.6
DNAJC19	Pam18, Tim14, TIMM14	Membrane	Mitochondrial membrane	116	12.5
DNAJC20	DNAJC20, HSC20, Jac1	Intracellular	Nucleoplasm, mitochondria, cytosol	235	27.4
DNAJC21	DNAJA5, GS3, JJJ1	Intracellular	Nucleus, nucleoli, cytosol	576	67.1
DNAJC22	FLJ13236, wus	Membrane	Vesicles	341	38.1
DNAJC23	SEC63, ERdj2, PRO2507, SEC63L	Membrane	Endoplasmic reticulum	760	88
DNAJC24	DPH4, JJJ3, ZCSL3	Intracellular	Cytosol	149	17.1
DNAJC25	bA16L21.2.1	Membrane	Nucleoplasm and additionally in cytosol	360	42.4
DNAJC26	GAK (cyclin G–associated kinase	Intracellular	Golgi apparatus and additionally in vesicles	1311	143.2
DNAJC27	RabJS, RBJ	Intracellular	Nucleoplasm and additionally in cytosol	273	30.9
DNAJC28	C21orf55, C21orf78	Intracellular	Golgi transport complex	388	45.8
DNAJC29	SACS, ARSACS, DKFZp686B15167, KIAA0730, PPP1R138, SPAX6	Intracellular	Cytosol	4579	521.1
DNAJC30	WBSCR18	Membrane	Mitochondrial membrane	226	26

Table 1 (continued)

Gene name	Other names	Cellular location	Subcellular location	Length (a.a.)	Mass (kDa)
Chaperonins/HSP60/HSPD					
HSPD1	HLD4, CPN60, GROEL, HSP60, HSPD1, HSP65, SPG13, HSP-60, HuCHA60	Intracellular	Mitochondria	573	61
CCT1	TCP1, CCTA, CCT-alpha, TCP-1-alpha, D6S230E	Intracellular	Cytosol, centrosome	556	60
CCT2	CCTB, CCT-beta, TCP-1-beta, HEL-S-100n, 99D8.1, PRO1633	Intracellular	Cytosol	535	57
CCT3	CCTG, CCT-gamma, TCP-1-gamma, TRiC5, PIG48	Intracellular	Plasma membrane, cytosol	545	61
CCT4	CCTD, CCT-delta, TCP-1-delta, SRB	Intracellular	Cytosol and additionally in nucleoplasm	539	58
CCT5	CCTE, CCT-epsilon, TCP-1-epsilon, KIAA0098, HEL-S-69, PNAS-102	Intracellular	Cytoplasm and cytoskeleton	541	60
CCT6A	CCT6, CCTZ, CCT-zeta, CCT-zeta1, TCP-1-zeta, HTR3, TCP20, TTCP20	Intracellular	Cytosol	531	58
CCT6B	CCTZ2, CCT-zeta2, TSA303	Intracellular	Cytosol	530	58
CCT7	CCTH, CCT-eta, TCP-1-eta, NIP7-1	Intracellular	Cytosol	543	59
CCT8	CCTQ, CCT-theta, TCP-1-theta, KIAA002, PRED71	Intracellular	Intermediate filaments and additionally in cytosol, nucleoplasm	548	60
HSP70/HSPA					
HSPA1A	HSP70.1, HSP70-1, HSP72, HSPA1, HSX70	Intracellular	Nucleoplasm, vesicles and additionally in cytosol	641	70
HSPA1B	HSP70.2, HSP70-2, HSP72, HSPA1, HSX70	Intracellular	Nucleoplasm, vesicles and additionally in cytosol	641	70
HSPA1L	HSP70-HOM, Hum70t, HSP70-1L	Intracellular	Vesicles and additionally in nucleoplasm	641	70
HSPA2	HSP70-2, HSP70-3	Intracellular	Vesicles and additionally in nucleoplasm	639	70
HSPA5	BiP, GRP78, MIF2	Intracellular	Cytosol	654	72
HSPA6	HSP70B'	Intracellular	Vesicles and additionally in nucleoplasm	643	71
HSPA8	HSC70, HSP73, HSC71, HSPA10	Intracellular	Nucleoplasm and additionally in vesicles	646	71
HSPA9	Mortalin, GRP75, mt-HSP70, HSPA9B	Intracellular	Mitochondria	679	74
HSPA12A	KIAA0417	Intracellular	Golgi apparatus, cytosol	675	75
HSPA12B	C20orf60	Intracellular	Nucleoplasm	686	76
HSPA13	STCH	Intracellular	Microsomes	471	52
HSPA14	HSP70L1, HSP60, HSP70-4,	Intracellular	Not known	509	55
HSP90/HSPC					
HSP90AA1	LAP2, HSP86, HSPC1, HSPCA, HSP89A, HSP89, HSP90, HSP90A, HSP90-alpha, Renal Carcinoma Antigen NY-REN-38, EL52, FLJ31884	Intracellular	Cytosol	854	98
HSP90AA2	LAP2, HSP86, HSPC1, HSPCA, HSP89A, HSP89, HSP90, HSP90A, HSP90-alpha, Renal Carcinoma Antigen NY-REN-38, EL52,	Intracellular	Cytosol	732	85
HSP90AB1	HSPC2, HSPCB, D6S182, HSP90B, HSP90-beta, HSP84	Intracellular	Cytosol	724	83
HSP90B1	ECGP, GP96, TRA1, GRP94, endoplasmin, HEL35, HEL-S-125m	Intracellular	Endoplasmic reticulum	803	92
TRAP1	HSP75, HSP90L	Intracellular	Mitochondria	704	80
HSP110/HSPH					
HSPH1	HSP110, HSP105A, HSP105B, KIAA0201, NY-CO-25	Intracellular	Cytosol and additionally in nucleoplasm	858	97

Table 1 (continued)

Gene name	Other names	Cellular location	Subcellular location	Length (a.a.)	Mass (kDa)
HSPH2	HSPA4, APG2, HSP70RY	Intracellular	Nucleoplasm, cytosol	840	94
HSPH3	HSPA4L, APG1, OSP94	Intracellular	Centrosome, cytosol	839	95
HSPH4	HYOU1, GRP170, ORP150, HSP12A	Intracellular	Endoplasmic reticulum	999	111

specific HSP isoforms during virus infection, this aspect has not been reviewed appropriately. In the present review, we have tried to put together our current understanding related to modulation and function of different isoforms of various HSP families during virus infection, focusing more specifically on HIV-1 infection.

Heat shock protein B (HSPB/sHSP family)

Small HSP (sHSP) are a group of ten (HSPB1-10) proteins having a molecular weight from 15 to 30 kDa, which are normally present as large oligomers at basal levels. They were first discovered in the chromosomal puffs of *Drosophila melanogaster* upon heat shock and ecdysterone treatment (Tissiéres et al. 1974). The members of this family have a conserved C-terminal domain, homologous to alpha crystallin of the vertebrate eye lens (Kim et al. 1998). The length of the C-terminus is highly flexible and has a conserved sequence, a IXI/V motif. The N-terminus domain, also called the WDPF domain (as it contains this amino acid sequence), is highly variable (Lelj-Garolla and Mauk 2006) (Fig. 2a). There are two alpha crystallin genes, alpha A and alpha B. These proteins are a major component of the vertebrate eye lens. In the early 1990s, it was discovered that alpha B crystallin is a small heat shock protein (Klemenz et al. 1991). Alpha A crystallin confers thermo-resistance to cells upon overexpression (van den Ijssel et al. 1994) and also acts as a molecular chaperone outside of its role as a major lens protein (Horwitz 1992).

HSP27 is one of the most studied members of the sHSP family. The protein is phosphorylated by p38 MAPK in vivo at multiple serine residues (Gaestel et al. 1991; Landry et al. 1992; Guay et al. 1997). It then forms smaller oligomers (Mehlen et al. 1997; Rogalla et al. 1999), and the phosphorylated form regulates many of its functions. HSP27 has been documented to respond to different types of cellular stress. During oxidative stress, it acts as an antioxidant by lowering reactive oxygen species by decreasing iron levels (Mehlen et al. 1997; Arrigo 2001; Arrigo et al. 2005). During chemical stress, HSP27 acts as an anti-apoptotic agent. It binds DAXX during Fas-FasL-mediated apoptosis (Charette and Landry 2000) and prevents mitochondria-dependent apoptosis by interacting with cytochrome c and indirectly inhibiting Bax (Bruey et al. 2000; Havasi et al. 2008). It has been observed that the levels of HSP27 significantly increase in many disease states such as renal injury, renal fibrosis, cancer, cardiovascular disease, neurodegenerative disease, and neuronal injury (Vidyasagar et al. 2012).

HSP27 has been implicated in viral infections also. In human adenovirus–infected cells, HSP27, p38 MAPK and NFκB-p65 form a signalling complex that affects downstream pro-inflammatory mediators (Rajaiya et al. 2012). HSP27 cellular localization is modified and reorganized during HSV-1

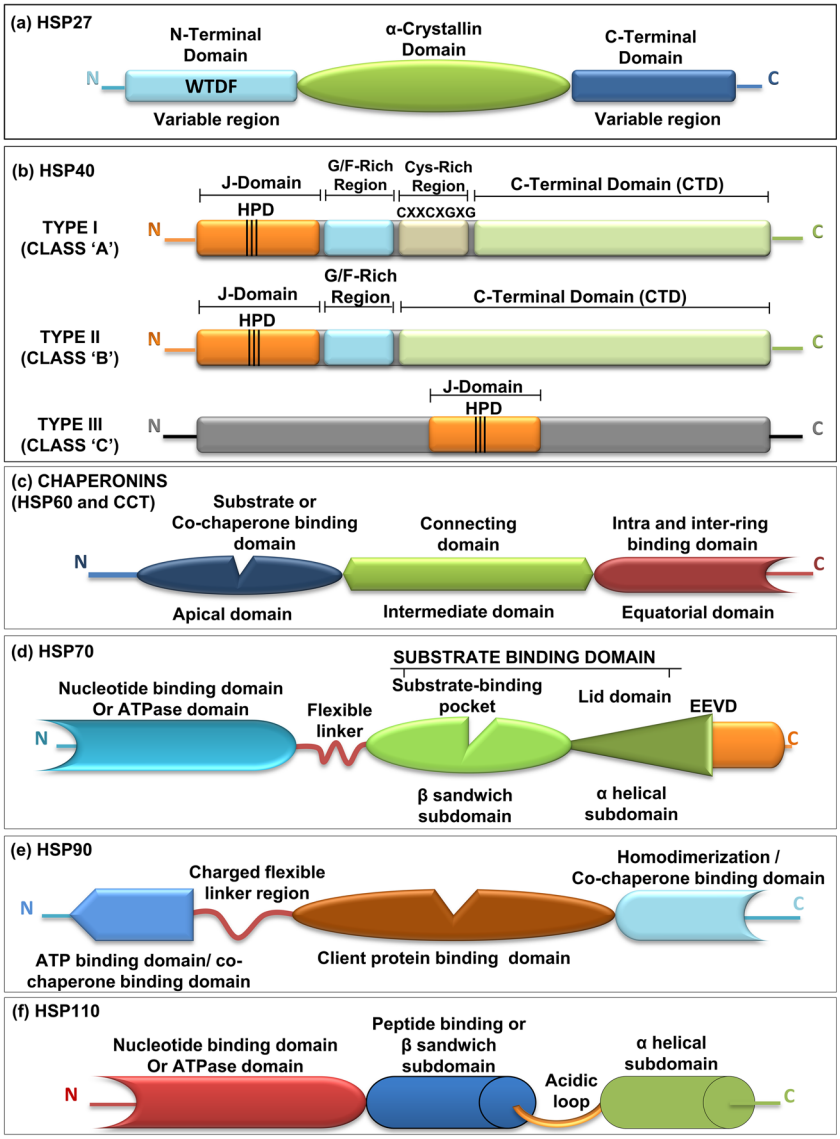

Fig. 2 Schematic representation of domain organization of different heat shock protein (HSP) families. Each HSP family consists of some common domains in all the members, such as in **a)** HSP27: N- and C-terminal variable regions, and an α-crystallin intermediate domain, **b)** HSP40: N-terminal conserved J-domain and C-terminal substrate-binding domain, **c)** chaperonins: N-terminal apical domain for substrate binding and C-terminal ring binding domain connected through the intermediate connecting domain, **d)** HSP70; N-terminal ATPase domain and C-terminal substrate-binding domain; **e)** HSP90; N-terminal ATP–binding domain, client protein–binding middle domain and C-terminal domain required for homo-dimerization and **f)** HSP110: N-terminal ATPase domain and C-terminal peptide–binding domain

infection, and furthermore, replication of the virus is drastically reduced upon depletion of the HSP27 (Mathew et al. 2009). The same is the case in Enterovirus (EV-A71) infection where HSP27 was increased upon infection whereas knockout of HSP27 results in reduced viral replication (Dan et al. 2019). The converse of what happens in other viruses occurs in swine fever virus wherein depletion of HSP27 increases virus replication. Ectopic expression reduces replication through activation of NF-κB signalling in PK-15 cells. HSP27 was also shown to interact with NS5A, a non-structural protein, as a response to viral replication and assembly (Ling et al. 2018). In hepatitis B virus, HSP27 levels are increased in infected human liver tissues and virus-producing HepG2.2.15 cells (Tong et al. 2013).

The studies on HSP27 in different viruses indicate its role as both a pro-viral and antiviral factor through various mechanisms involving different signalling pathways. On the other hand, work done on the role of sHSPs or even HSP27 in HIV-1 infection is quite limited. In an early study, it was shown that in HIV-1 chronically infected monocytic and lymphocytic $CD4^+$ T-cell lines, there is a 2- to 15-fold increase in HSP27 production (Brenner et al. 1995). They also showed that there is an early increase in HSP27 mRNA and protein, which is short-lived and declines during initiation of de novo viral synthesis. The levels again rise in the late stages of infection when there is maximal viral production and CD4 cytolysis (Wainberg et al. 1997). In 2007, Liang et al. investigated cellular proteins that can suppress the viral protein R (Vpr) function of HIV-1. Increased levels of HSP27 inhibit Vpr-induced cell cycle G2 arrest (Liang et al. 2007), and activation of HSP27 by Vpr is mediated through HSF1. HSP27 seems to suppress Vpr activities, and Vpr in turn inhibits a prolonged expression of HSP27 in heat shocked cells. The role of HSP27 in other virus infections through NF-κB has

been highlighted earlier, and NF-κB is also central to the functions of HIV-1 Vpr during the virus life cycle (Varin et al. 2005; Kogan et al. 2013). However, the link between HSP27, NF-κB and Vpr, if any, has not yet been well explored and may be worth looking into. CD8+ CD57+ lymphocytes, a population that expands during HIV infection and other chronic conditions, show a constitutive expression of HSP27 (Wood et al. 2010). Low HSP27 levels coincided with increased apoptosis of the cells and vice versa. Apart from showing the early induction of HSP27 during HIV-1 infection, Brenner and Wainberg also indicated the role of HSP27 and HSP70 as vaccine adjuvants due to their ability to interact with viral proteins and also redistribute themselves to the surface of the plasma membrane (Brenner and Wainberg 1999). In 2017, Milani et al. further added to this body of work, by illustrating the use of HSP27-Nef fusion DNA or protein to elicit high humoral and cellular immune responses (Milani et al. 2017, 2020). Further exploration in this area could help the HIV-AIDS community in developing a vaccine.

The literature on the role of alpha crystallins (HSPB4 and HSPB5) on HIV pathogenesis is very limited. One study reported that alpha crystallins bound to calcium ions assist in the folding of HIV-1 protease through a molten-globule-like intermediate (Dash et al. 2005). Another isoform of the sHSP family, HSPB8 regulates Sam68, a protein that enhances Rev response element–mediated gene expression and viral production. HSPB8 actually inhibits the function of Sam68 in this pathway through its binding with Sam68 (Badri et al. 2006). Further studies in elucidating the role of these sHSP isoforms in virus infection could be very useful.

DNAJ family (HSP40)

The HSP40/DNAJ (heat shock protein 40) family is defined as a group of proteins that are orthologs of the *E. coli* HSP40 (DNAJ) protein. The DNAJ/HSP40 family belongs to a diverse group of co-chaperones which assists HSP70 for proper protein folding, protein transport and degradation. DNAJ/HSP40 physically interacts with HSP70 through its conserved J domain and increases the ATPase activity of HSP70 (Cheetham and Caplan 1998). DNAJ/HSP40 is reported to be located in many subcellular compartments such as mitochondria, endoplasmic reticulum, cytosol, nuclei, endosome and ribosomes and extracellular environment of eukaryotes and cytosol of prokaryotes (Fan et al. 2003; Walsh et al. 2004; Qiu et al. 2006; Kampinga and Craig 2010). DNAJ/HSP40 plays a vital role in the expression of genes, initiation of translation, translocation, degradation and folding/unfolding of proteins. It binds to unfolded or non-native polypeptides and prevents their aggregation (Fan et al. 2003). DNAJ/HSP40 is also linked with folded proteins, which results in the "remodelling" of large multi-protein complexes and hence thought to be regulating the balance of protein/protein interactions (Kampinga and Craig 2010).

The human genome encodes about 49 isoforms of DNAJ/HSP40 protein, which show significant diversity at the primary sequence level. These isoforms show variability in the size which ranges from ~10 kDa (DNAJC19) to ~504 kDa (DNAJC29). The DNAJ/HSP40 protein consists of four typical domains, an N-terminal highly conserved sequence of about 70 amino acids known as signature J-domain, followed by a Gly/Phe-rich region (G/F-rich domain), zinc finger domain (four repeats of the CxxCxGxG type) and a less conserved C-terminal substrate–binding domain. The members of the DNAJ/HSP40 family have been categorized majorly into three groups: type I (group A) proteins comprise all four domains; in type II (group B) proteins, the zinc-finger domain is absent; and type III (group C) proteins retain only the signature J-domain, located at any position in the protein sequence (Fig. 2b).

The DNAJ/HSP40 family has been implicated in various human diseases like neurodegenerative disorders (Muchowski et al. 2000; Sherman and Goldberg 2001), autoimmune diseases (Albani et al. 1995; Chukwuocha et al. 1999; Tukaj et al. 2010), cancer (Mitra et al. 2009) and microbial infections (Neckers and Tatu 2008). DNAJ/HSP40 family members are found to be modulated during various neuro-degenerative diseases like DNAJB6 in Huntington's disease (Orr and Zoghbi 2007; Wetzel 2012; Månsson et al. 2014) and DNAJC13 in Parkinson's disease (Rajput et al. 2015). Various reports also show that few members of the DNAJ family are associated in different types of cancers such as DNAJC15 in human ovarian tumours (Shridhar et al. 2001), DNAJA3 in gliomas (Trentin et al. 2004) and colon cancer (Kurzik-Dumke et al. 2008), DNAJB4 in lung cancer (Tsai et al. 2006) and DNAJC12 in breast tumours (De Bessa et al. 2006).

In case of viral infections, the HSP40/DNAJ family has been identified to regulate the replication of various viruses. Although the HSP40 family comprises several members, it has been earlier considered and represented as one protein in several studies. In one such report, it was shown that HSP40 interacts with matrix protein (M2) and $p58^{IPK}$ protein of influenza virus (A/B) and regulates PKR signalling pathway in influenza-infected cells (Melville et al. 1997; Guan et al. 2010). In case of hepatitis B virus infection, HSP40 helps in the priming and activation of reverse transcriptase enzyme and enhances the viral replication (Beck and Nassal 2003, 2007). HSP40 has also been reported to interact with the 3′ end of RNA of murine hepatitis virus to possibly promote its stability (Nanda et al. 2004). Similarly, HSP40 interaction with the nucleotide-binding domain (NBD) of HSP70 is crucial for its stronger binding with viral nucleocapsid protein, which stimulates the transcription and genome replication of measles virus (Couturier et al. 2010). HSP40 was also shown to interact with E1 helicase of human papillomavirus and enhance its

binding to the origin of DNA replication (Liu et al. 1998; Lin et al. 2002). Similarly, in case of herpes simplex virus-1 infection, HSP40 enhances the binding of viral initiator protein (UL9) with origin of the DNA replication site and stimulates viral replication (Le Gac and Boehmer 2002).

As is the case with other heat shock protein families, studies on the isoform-specific role of the HSP40 family has emerged only since the early 2000s. Some of the DNAJ/HSP40 family isoforms have been reported to regulate the pathogenesis of several viruses. It has been reported that DNAJA1 associates with the bPB2 and PA subunits of RNA-dependent RNA polymerase (RdRp) of the influenza A virus through its C-terminal substrate–binding region and translocate into the nucleus to enhance viral RNA synthesis independent of HSP70 (Cao et al. 2014). DNAJA1 is also reported to regulate the replication of Japanese encephalitis virus through interacting with nonstructural protein 5 (NS5). Overexpression of DNAJA1 increases viral RNA synthesis in infected cells (Wang et al. 2011). DNAJA3 regulates human T-cell leukaemia virus type 1 (HTLV-1) replication through interaction with Tax, an oncogenic viral protein encoded by HTLV-1 that induces cellular transformation of T- lymphocytes (Cheng et al. 2002). In case of adenovirus infection, DNAJB1 is activated by Gam-1, a viral encoded protein that regulates viral replication by activating heat shock response (Glotzer et al. 2000). There is another report which shows that DNAJB6 and DNAJA1 inhibit hepatitis B virus replication and capsid assembly through accelerated degradation of the viral core and HBx proteins (Sohn et al. 2006). In HBV, DNAJB6 enhances the reverse transcription through binding with Hsc70 independent of HSP90 and other co-factors (Beck and Nassal 2003, 2007). DNAJB11, DNAJB12, DNAJB14 and DNAJC18 seem to regulate simian virus (SV40) replication. This virus utilizes ER-localized proteins to initiate disassembly and transit through the cell (Goodwin et al. 2011). DNAJC14 is recruited to the replication complexes of yellow fever virus and inhibits viral RNA replication (Yi et al. 2011). Later on, researchers have also shown that HSP40 plays an important role in different steps of the dengue virus life cycle by assisting HSP70 function. They highlighted nine distinct isoforms of HSP40 which are involved at different stages of the virus life cycle; of these, DNAJB11 promotes viral RNA synthesis, while DNAJB6 associates with viral capsid protein and facilitates virion biogenesis (Taguwa et al. 2015).

In case of HIV-1 infection, there are only few reports which show the importance of the HSP40 family or its members in virus replication or infection progression. Our lab has earlier shown that HIV-1 Nef protein interacts with HSP40 and increases its translocation into the nucleus of infected cells. The isoform involved seems to be DNAJB1. This interaction with Nef enhances the long terminal repeat-mediated viral gene expression by becoming part of the cyclin-dependent kinase 9-associated transcription complex (Kumar and Mitra 2005). Apart from this, HSP40 also interacts with HSP70 and they regulate HIV-1 replication in a reciprocal manner where HSP70 acts as an antiviral factor and HSP40 acts as a proviral factor (Kumar et al. 2011). There are a few recent studies in which people have shown the isoform-specific role of HSP40 in HIV-1 infection. DNAJ/HSP40 family members such as DNAJB1, DNAJB6, DNAJA1 and DNAJC5 were shown to negatively regulate the HIV-1 replication by downregulating Rev viral protein expression in one study (Urano et al. 2013). The DNAJB6-large variant (MRJ-L) interacts with HIV-1 Vpr and regulates HIV-1 replication. An increase in DNAJB6 levels efficiently increases the HIV-1 replication or reduction in DNAJB6 expression decreases HIV-1 production significantly (Chiang et al. 2014; Ko et al. 2019). In case of HIV-2 infection, DNAJB6 protein interacts with Vpx protein of virus and helps in the nuclear import of the pre-integration complex (PIC). DNAJB6 competes with the Gag precursor protein for the binding of Vpx and enhances the nuclear import of PIC (Cheng et al. 2008). Recently, our laboratory has shown that during heat stress, only DNAJA4, DNAJB1 and DNAJB4 were upregulated, while during HIV-1 infection, several HSP40 isoforms showed significant upregulation in mRNA expression levels (Chand et al. 2021). Modulation of so many isoforms piqued interest in whether all the modulated isoforms are involved in regulating virus replication and infection progression differently or it is just because of the stress induced by virus infection.

Due to the vast number of isoforms present in the HSP40 family, any work done regarding the same only seems to reflect a fraction of the potential of HSP40 isoforms in viral infections. However, our recent study on the expression modulation of these different isoforms during HIV-1 infection makes it all the more necessary to do their further functional characterization.

Chaperonins

The family is specifically termed “chaperonin” that represents a particular class of chaperones with a large multimeric double-ring-like cylindrical structure. This structure allows the sequestration of newly synthesized and denatured proteins inside the central cavity for their folding with the help of ATP hydrolysis. The chaperonins are divided into two distantly related subfamilies—group I and group II. The general domain arrangement consists of an N-terminal apical domain needed for peptide binding and recognition. The C-terminal equatorial domain helps in the binding of each subunit and has most of the ATP contact sites. The intermediate domain links the two domains. This regulates the conformational change of the chaperonin (Dun et al. 2012) (Fig. 2c). The group I members are present in Eubacteria (GroEL), and in eukaryotic organelles of eubacterial descent i.e. mitochondria (HSP60/

HSPD/Cpn60) and chloroplasts (in plants) (Hemmingsen et al. 1988; Mayer 2010; Saibil 2013). The most well-studied member of the group I chaperonin is *Escherichia coli* GroEL (~ 57 kDa) with a double heptameric ring structure (Hohn et al. 1979; Hendrix 1979; Braig et al. 1994). Following ATP binding, GroEL recruits its single-ring co-chaperonin GroES (~10 kDa) of the same symmetry to form functional bacterial chaperonin complex GroEL-GroES. The co-chaperonin caps the central cavity of the complex, inducing structural rearrangements for transition from the open ring to a closed container for protein folding (Chen et al. 1994; Xu et al. 1997). Unlike the bacterial homolog, the structure and function of the mammalian chaperonin system HSP60-HSP10 have remained unclear. Following mitochondrial import, the mature form of HSP60 (~58 kDa) is primarily involved in mitochondrial protein folding (Cheng et al. 1989; Ostermann et al. 1989) and mitochondrial quality control (Magnoni et al. 2014). Extramitochondrial localizations of HSP60 have also been reported in some studies. The chaperonin has also been found on the surface of both normal (Soltys and Gupta 1997) and tumour cells (Piselli et al. 2000; Feng et al. 2002). Expression of surface HSP60 on stressed or damaged cells acts as a danger signal that further elicits pro-inflammatory response through the innate immune system (Ohashi et al. 2000). Similarly, apoptotic tumour cells exhibit an elevated surface expression of HSP60 as an immune biomarker resulting in stimulation of dendritic cells and generation of potent antitumor-specific T-cell responses (Feng et al. 2002). In addition to its intracellular and surface localizations, HSP60 has also been reported in extracellular space and in circulation. The extracellular HSP60 is associated with both pro- and anti-inflammatory effects through its engagement with several cell surface receptors such as Toll-like receptors (Cohen-Sfady et al. 2005, 2009). The group II chaperonin comprises archaeal thermosome (Phipps et al. 1991, 1993; Andrä et al. 1996) and eukaryotic cytosolic chaperonin called CCT (chaperonin-containing TCP1) or TriC (TCP1 ring complex) (Frydman et al. 1992; Gutsche et al. 1999). Members of this subfamily are composed of oligomeric eight- to nine-membered rings with each subunit weighing about ~52–65 kDa (Frydman et al. 1992; Phipps et al. 1993; Andrä et al. 1996; Ditzel et al. 1998). Unlike group I members, members of group II chaperonins have a built-in lid that encapsulates the substrates within the central folding chamber upon ATP binding and does not require a general co-chaperonin for their folding activity (Ditzel et al. 1998; Meyer et al. 2003; Douglas et al. 2011). The large oligomeric complex CCT is composed of two stacked identical rings of eight subunits (CCT1-8), each of which has a role in cytosolic protein folding and assembly through ATP hydrolysis (Bigotti and Clarke 2008). After its discovery, the chaperoning role of CCT had been implicated in biogenesis of cytoskeletal proteins, β-actin and tubulin (Gao et al. 1992; Yaffe et al. 1992).

A diverse range of functions of HSP60 in viral pathogenesis has been reported over the years. However, its immunomodulatory role has remained one of the most important and studied areas. The pro-viral effect of HSP60 in dengue virus infection is attributed to its elevated expression in infected human monocytic U-937 cells that leads to suppression of antiviral cytokine IFN-α (Padwad et al. 2009). HSP60 induces mitochondrial stress and enhances microglial production of pro-inflammatory cytokine IL-1β by activating NLRP3 inflammasome complex in Japanese encephalitis virus (JEV) infection (Swaroop et al. 2018). Production of soluble HSP60 (sHSP60) has been reported from hepatitis B virus (HBV)–infected replicating hepatocytes. sHSP60 enhances the frequency and function of HBcAg-specific interleukin-10 secreting regulatory T (T_{reg}) cells indicating the immune-suppressive role of sHSP60 (Kondo et al. 2010). Furthermore, this chaperonin is also involved in the regulation of apoptosis in viral pathogenesis. The anti-apoptotic nature of HSP60 is exemplified in hepatitis C virus (HCV) infection. Inactivation of HSP60 through its interaction with HCV core protein participates in the pathogenesis of HCV infection by induction of ROS generation and amplification of TNF-α-mediated cell death (Kang et al. 2009). HSP60 and co-chaperonin HSP10 together decrease the apoptotic potential of ectromelia virus–infected murine L929 fibroblasts by maintaining mitochondrial protein homeostasis, playing a role in altering the ratio of apoptotic proteins Bax, Bcl-2, and Bcl-xL (Wyżewski et al. 2019). In contrast to the previous two cases, this chaperonin exerts a pro-apoptotic effect in case of rotavirus (RV) SA11 and HBV infection. mtHSP60 is tyrosine-phosphorylated by the activated form of Src kinase with its subsequent ubiquitin-mediated proteasomal degradation during the early hours of RV-SA11 infection. The proteasomal degradation of mtHSP60 is inversely correlated with premature mitochondrial import of rotaviral pro-apoptotic factor nonstructural protein 4 (NSP4) that further delays early apoptosis (Chattopadhyay et al. 2017). In case of HBV infection also, the binding of HSP60 with hepatitis B virus X protein (HBx) has been shown to facilitate the HBx-mediated apoptosis (Tanaka et al. 2004). Viral infection and autoimmunity contribute to the pathogenesis of many autoimmune diseases. The molecular mimicry between viral antigens and host HSP60 is reported to be involved in the development of autoimmune diseases such as atherosclerosis and insulin-dependent diabetes mellitus (IDDM) or type 1 diabetes (T1D). The ability of the antibodies against human cytomegalovirus to cross-react with certain HSP60 epitopes that might amplify endothelial cell damage and the prevalence of these autoantibodies against HSP60 in most atherosclerotic patients have been correlated with the severity of this disease (Bason et al. 2003). The immunological cross-reaction between enterovirus capsid proteins and HSP60 of insulin-producing beta cells as autoantigens leads to destruction of

these cells, playing a role in etiopathogenesis of IDDM (Härkönen et al. 2000). Similarly, the molecular mimicry of glycoproteins E (gE) of varicella virus and hemagglutinin of measles virus with host HSP60, particularly in diabetics with genetic predisposition of HLA DR3/DR4, are also involved in etiopathology of T1D (Meziane et al. 2020). Moreover, Ebola virus infection also induces secretion of autoantibodies against HSP60, which is a causative parameter of various serious autoimmune disorders observed in Ebola survivors (Fausther-Bovendo et al. 2017). In addition to previously mentioned functions, this chaperonin also interacts with other viral factors. HSP60 has also been identified as a chikungunya virus (CHIKV)–interacting protein that might play a role in CHIKV entry into the host cells (Wintachai et al. 2012). Similarly, HSP60 has been demonstrated to interact with human hepatitis B virus (HBV) polymerase that is important for maturation of this enzyme to active state (Park and Jung 2001). Furthermore, HSP60 has also been demonstrated to be a part of stable RNA-protein complex consisting murine hepatitis virus (MHV) RNA along with mitochondrial-aconitase, mitochondrial HSP70 and HSP40 (Nanda et al. 2004).

Of the eight subunits of eukaryotic cytosolic chaperonin CCT, many have been reported to participate in the biological cycle of different viruses. The chaperonin TCP-1 (also known as CCT1) or a related protein has been reportedly associated with HBV core polypeptides in two different intermediates in viral assembly (Lingappa et al. 1994). CCT2 interacts with influenza virus RNA polymerase subunit PB2 where it is suggested to act as chaperone for PB2 and its incorporation into RNA polymerase complex (Fislová et al. 2010). The CCT3 aids in the proper folding of newly synthesized Gag polyprotein of Mason-Pfizer monkey virus (M-PMV) through its association with p4 and pp24/16-p12 domains of nascent Gag molecules. This further allows the intermolecular interactions between correctly folded Gag molecules for proper assembly of M-PMV capsid (Hong et al. 2001). In case of neurotropic rabies virus (RABV) infection, CCT3 positively regulates intracellular viral replication after being recruited to Negri bodies with the help of a complex comprising viral N and P proteins (Zhang et al. 2013). The Epstein-Barr virus (EBV) encoded a nuclear and transformation-related protein, EBNA-3, showing an association with CCT5 for its initial folding (Kashuba et al. 1999). CCT5 helps in the replication of hepatitis C virus (HCV) through its interaction with viral RNA polymerase NS5B (Inoue et al. 2011). The avian CCT5 has been demonstrated to bind with influenza A virus (IAV) nucleoprotein (NP) as well as polymerase basic protein 1 (PB1) and polymerase basic protein 2 (PB2). Moreover, the elevated expression of CCT5 benefits the viral infection by promoting nuclear export of NP as well as activity of the viral polymerase (Zhang et al. 2020). The identification of CCT7 as a binding partner of the capsid protein hexon of Fowl adenovirus serotype 4 (FAdV-4) suggests its function in viral replication (Gao et al. 2019). The chaperonin CCT8 plays a role in the post-translocational refolding of tobamovirus-transported proteins, thus facilitating the spread of viral infection (Fichtenbauer et al. 2012).

HSP60 has been co-purified with HIV virus preparation which suggests a specific association between this chaperone and viral factors encapsidated into HIV particles (Bartz et al. 1994). Later, HSP60 was identified as an interacting partner of HIV transmembrane glycoprotein gp41 (Speth et al. 1999). The co-expression of two subunits of HIV-1 reverse transcriptase (HIV-1 RT) i.e. p66 and p55, with *Escherichia coli* chaperonin complex GroEL-GroES in *E. coli*, reportedly improved the yield and nucleic acid–binding activity of HIV-1 RT (Maier et al. 2000). The human HSP60 has been demonstrated to interact with the catalytic core domain of HIV-1 integrase (IN) and is also able to stimulate the IN activity. Moreover, the viral IN was also recognized as a substrate by the functional human HSP60-HSP10 complex in presence of ATP (Parissi et al. 2001). The level of circulating HSP60 has been found to be elevated in HIV-infected patients which was significantly reduced following anti-retroviral therapy (Anraku et al. 2012). Furthermore, CCT5 also exhibited a strong association with HIV-1 p6 protein in the yeast two-hybrid system (Hong et al. 2001).

Despite the extensive reports on function of HSP60 at different stages of viral pathogenesis, there have been limited studies on its role in HIV infection. Previously, mitochondrial stress has been reported in HIV infection (Pérez-Matute et al. 2013; Var et al. 2016) which raises the possibility of involvement of HSP60 in mitochondrial quality control during the course of infection. The function of HSP60 in immune modulation has also not been looked into in case of HIV infection. Though HIV-1 RT and gp41 have been identified as an interacting partner of this chaperonin, the functional significance of this association has remained unclear. Likewise, the binding of CCT5 with HIV-1 p6 protein has not been further characterized. Considering the well-studied roles of HSP60 and CCT in viral pathophysiology, future studies on the effect of the chaperonin system in HIV pathogenesis might be able to contribute significantly in this area.

HSPA family (HSP70)

The 70-kDa heat shock protein (HSP70) is one of the most conserved HSPs throughout the evolution, and its members are found in several intracellular compartments such as endoplasmic reticulum (HSPA5), mitochondria (HSPA9) and nucleus (HSPA1A and HSPA8). In unstressed cells, HSP70 forms 0.5 to 2% of the protein mass (Finka and Goloubinoff 2013). Like most other HSPs, HSP70 is well established to function as a chaperone in protein folding, translocation,

refolding and degradation (Finka et al. 2015a). It is also known to interact with components of various signalling pathways, thereby affecting growth and development (Nollen and Morimoto 2002). HSP70 is also well documented to play an anti-apoptotic role (Jäättelä et al. 1998). The HSP70 family has an N-terminal ATPase domain (nucleotide-binding domain) and a C-terminal substrate–binding domain. The C-terminal domain is subdivided into a β sandwich subdomain and a α helical subdomain (Mayer and Bukau 2005) (Fig. 2d). The primary functions of HSP70 are dependent on its ATPase cycle. Normally, HSP70 is present in two states. One form is the ATP bound state that has low affinity for substrates and high substrate association and dissociation rates. The other form is the ADP-bound state that has high affinity for substrates but low substrate association and dissociation rates. The catalysis of ATP to ADP occurs through the low, intrinsic ATPase activity of HSP70. This activity is highly enhanced by HSP40 co-chaperones also called J domain proteins (JDP) (Minami et al. 1996). The exchange of ADP with ATP is catalyzed by nucleotide exchange factors such as HSP110 and heat shock protein–binding protein (Bracher and Verghese 2015).

HSP70 has 13 different isoforms in human cells that are found in several intracellular compartments. HSPA8 is a constitutive isoform, making up about 50% of the HSP70 family and found in the cytoplasm and nucleus (Finka and Goloubinoff 2013). HSPA1A, an inducible member, is found in low amounts in unstressed cells. However, upon stress, an increase in HSPA1A makes it an abundant HSP70 isoform (Finka et al. 2015b). HSPA1A is found on chromosome 6 in the major histocompatibility complex (MHC-III) region along with another identical heat-inducible HSP isoform called HSPA1B (Milner and Duncan Campbell 1990). HSPA1L is found on the same chromosome 6 as HSPA1A and HSPA1B and is constitutively expressed in human testicular cells (Milner and Duncan Campbell 1990; Ito et al. 1998). HSPA5, found in the endoplasmic reticulum (Haas and Wabl 1983), and HSPA9, found in the mitochondria (Domanico et al. 1993; Bhattacharyya et al. 1995), form the next abundant members of the HSP70 family. HSPA6 (Leung et al. 1990) and HSPA7 (Voellmy et al. 1985) are highly similar, heat-inducible isoforms. HSPA12A and HSPA12B are distant members of the HSP70 family since they have an atypical ATPase domain. They were first found in the atherosclerotic lesions of mice (Han et al. 2003). HSPA13 is a non-heat-inducible member of the HSP70 family expressed in all human cell types (Otterson and Kaye 1997). HSPA14 is the last member of the HSP70 family and is found in dendritic cells and has enhanced Th1-polarizing activity (Wan et al. 2004).

The change in expression and role of HSP70 in viral infections has been widely documented. Most of the earlier studies concentrated on the inducible HSP70 isoform HSPA1A (HSP72, HSPA1) and the constitutive isoform HSPA8 (HSC70, HSC71). For example, there is an increase in HSP70 levels during West Nile viral infection (Pastorino et al. 2009). HSC70 associates with and helps in folding of the capsid proteins of polyomavirus. This possibly prevents premature virion assembly and helps in the capsid translocation into the nucleus (Cripe et al. 1995; Chromy et al. 2003). HSC70 is also involved in the life cycle of HPV at different steps of HPV DNA replication and is also required for nuclear localization of L2. HSC70 associates with L2 capsid protein of HPV as an intermediate for virus assembly (Florin et al. 2004). It is also associated with the influenza virus matrix protein 1, which is important for virus replication, assembly and budding (Watanabe et al. 2006). Studies show that HSP72 also interacts with NS5A, NS3 and NS5B replication proteins of HCV (Chen et al. 2010). The role of the HSP70 family in HCV replication was corroborated by other studies in which quercetin was used to knock down HSP70 mRNA transcription that resulted in reduced HCV accumulation and particle production (Gonzalez et al. 2009). Vaccinia virus infection induces HSP70, and there is an association of HSP70 with viral proteins suggesting their involvement in virus assembly (Jindal and Young 1992). Rabies virus infection also induces HSP70 expression, and HSP70 is required at different stages of the virus life cycle (Lahaye et al. 2012). Recent studies show that the regulatory leader RNA of rabies virus interacts with HSC70 and downregulates virus replication (Zhang et al. 2017).

Studies on the isoform-specific roles of HSP70 in viral infections were limited to the inducible HSP70 and constitutive HSC70 initially but have picked up in the last several years in roles of the other isoforms. For instance, filoviruses differentially exploit HSPA5. The mature virions of Ebola viruses contain HSPA5 whereas the Marburg viruses lack the presence of HSPA5 in the mature virions. Also, siRNA knockdown of HSPA5 reduces the cells infected with Ebola and Marburg virus. Further, knockdown also inhibits the release of new Ebola and Marburg virus particles (Spurgers et al. 2010; Patrick Reid et al. 2014). HSPA5 is also implicated in several hepatitis virus infections. Hepatitis C virus non-structural protein 5A (NS5A) interacts with HSPA5 and enhances its expression in hepatocytes (Jiang et al. 2014). HSPA5 is further reported to play an antiviral role in Hepatitis A virus infection (Jiang et al. 2017). Human cytomegalovirus is another virus that induces HSPA5 transcription and translation (Buchkovich et al. 2008, 2009, 2010). Taguwa et al. in 2015 showed the requirement of HSPA8 in the dengue virus life cycle such as in entry, RNA replication and virion biogenesis (Taguwa et al. 2015). The same group showed that Zika virus depends on HSPA1A and HSPA8 to complete its life cycle (Taguwa et al. 2019). In case of Enterovirus A71 virus infection, HSP70 isoforms such as HSPA1A, HSPA8 and HSPA9 are required at all steps of the virus life cycle (Su

et al. 2020). In the current pandemic caused by SARS-CoV-2, early studies have suggested that HSPA5 is an important factor for the virus infection (Ha et al. 2020; Ibrahim et al. 2020).

As is the case in most viral infections, the role of HSP70 in HIV-1 infection has been also analyzed to a great extent. A short study by Furlini et al. in 1993 indicated that there is nuclear translocation of HSP70 upon interaction between CD4+ and HIV-1 gp120. Also, the newly synthesized HSP70 is mainly derived from constitutively expressed mRNA stored in the cytoplasm (Furlini et al. 1994). HSP70 mRNA is upregulated in CD4+ T cells infected with HIV-1 (Wainberg et al. 1997), and the expression of HSP70 is significantly increased in lymphocytes from HIV-1-infected subjects (Agnew et al. 2003). Later, it was shown that HSP70 is incorporated into HIV-1 virions and HIV-1 gag protein is sufficient for this phenomenon (Gurer et al. 2002). However, the role of the incorporated HSP70 has not yet been elucidated in detail. It could be involved in the viral uncoating process post viral entry or it could bind to the nascent gag protein during transport to the plasma membrane. Recombinant *Mycobacterium tuberculosis* HSP70 shows a dose-dependent inhibition on HIV-1 infection of CD4+ T cells, and combining HSP70 with a monoclonal antibody to CCR5 showed a very high percentage of inhibition at 99.7% (±0.9%) (Babaahmady et al. 2007). It is known that the tripartite motif 5α (TRIM5α) is a cellular protein that restricts HIV-1 at the early post-entry step (Nisole et al. 2005). Further studies are needed to understand what role HSP70 plays in the TRIM5α restriction of HIV. A study in 2011 showed that Nef suppressed HSP70-mediated Tat activation and the suppressing effect is dependent on HSP70 expression (Sugiyama et al. 2011a). The same group also showed that HSP70 inhibits the ubiquitination and degradation of APOBEC3G by Vif (Sugiyama et al. 2011b). HSP70 also seems to be induced in HIV-infected cells to target HIV-1 Vpr and reduce Vpr-dependent G2 arrest and apoptosis (Iordanskiy et al. 2004b). Iordanskiy et al. also showed that HSP70 stimulates nuclear import and replication in Vpr-deficient HIV-1 infected cells, basically taking over the function of Vpr. Interestingly, however, it has been reported to inhibit translocation of Vpr into the nucleus of wild-type infected cells (Iordanskiy et al. 2004a).

The isoform-specific roles of HSP70 are being actively investigated in the past decade. In 2009, Bushman et al. released a meta-analysis of 9 different genome wide studies that were performed to identify common host factors involved in HIV-1 replication (Bushman et al. 2009). HSPA5 was noted to interact with the envelope protein during its folding in the endoplasmic reticulum (Earl et al. 1991), and other isoforms were implicated to interact with viral proteins like Tat, Gag and Vpr. HIV-1 Clade B gp120 induces HSPA5 and other ER stress markers, as compared to HIV-1 Clade C gp120 in astrocytoma cells (López et al. 2017). HIV-1 tat is also known to induce HSPA5 and other ER stress markers (Ma et al. 2016). HSPA9 or mortalin was shown to be required for Nef secretion in exosomes (Shelton et al. 2012). Independently, another group showed the interaction of HSPA9 and Nef through a yeast two-hybrid screen (Kammula et al. 2012). A very systematic review of literature until December 2016 identifying various "candidate inhibitory factors" of HIV-1 infection was published in 2018 (Gélinas et al. 2018). Several HSP40, HSP70 and HSP90 isoforms were implicated in different stages of the virus life cycle. While the role of HSP70 isoforms in HIV-1 infection is better characterized than other HSP families, it still needs to be fully explored. For example, while HSPA8 has been indicated to play vital roles in replication and viral assembly in other viral infections, its role in HIV-1 infection remains to be clearly elucidated. In another instance, HSPA2 and HSPA1L have not been characterized either in other viral infections or in HIV-1 infection. Due to their enrichment in testis tissue, they may play a vital role in HIV-1 entry. Added to that, the direct roles of the distant HSP70 members HSPA12, HSPA13 and HSPA14 in HIV-1 infection have not at all been looked into, even though HSPA13 was shown to possibly interact with the Env protein (Luo et al. 2016). Another aspect that needs to be understood is the implication of HSP70-HSP40-HSP90 interactions during HIV-1 infection.

HSPC family (HSP90)

HSP90 (heat shock protein, 90 kDa) is a vital, evolutionarily conserved and the most abundant member of the HSP family, making up to 1–2% of the total cellular proteins (Csermely et al. 1998). Unlike other members of the HSP family, HSP90 interacts with specific classes of substrates which majorly comprises kinases and steroid hormone receptors (Riggs et al. 2004). Dimerization of HSP90 is vital for its essential ATPase activity where each monomer consists of an N-terminal nucleotide-binding domain, a middle domain that binds to the client proteins and a C terminal dimerization domain (Schopf et al. 2017) (Fig. 2e). In the cytoplasm, HSP90 is expressed as stress-inducible isoform HSP90α that includes two transcript variants i.e. HSP90AA1 and HSP90AA2, and one constitutive isoform HSP90AB1/HSP90β. These cytosolic isoforms are involved in the activity, maturation, stabilization and turnover of a huge set of substrates (Stechmann and Cavalier-Smith 2004; Chen et al. 2005; Zuehlke et al. 2015). Other than the cytosolic variants, one HSP90 isoform is present in endoplasmic reticulum (ER) as HSP90B1 (other names are endoplasmin, Grp94, gp96, TRA1) and one in mitochondria as tumour necrosis factor receptor-associated protein-1 (TRAP1) (Ho Yeong Song et al. 1995; Stechmann and Cavalier-Smith 2004; Chen et al. 2005). Apart from being a peptide-binding protein, HSP90B1

is also important in Ca^{2+} homeostasis, ER stress response and host defence (Randow and Seed 2001; Eletto et al. 2010). TRAP1 is known for its role in protection against oxidative stress and apoptosis (Masuda et al. 2004; Hua et al. 2007; Im et al. 2007).

HSP90 has been known to play a role in viral protein folding for several different viruses. The chaperone activity of HSP90 is also important for maturation and maintenance of viral proteins including polymerases, capsids and cell attachment factors through interaction. This behaviour is exemplified by the role of HSP90 in folding of viral L polymerase in measles and Nipah virus (Bloyet et al. 2016), as well as in stabilization of the L protein in La Crosse virus (Connor et al. 2007), mumps virus (Katoh et al. 2017) and vesicular stomatitis virus (Connor et al. 2007). It participates in capsid precursor processing and capsid assembly of picornaviruses, including coxsackievirus, poliovirus and rhinovirus (Geller et al. 2007). The chaperone is reportedly involved in biogenesis of reovirus cell attachment factor σ1 (Gilmore et al. 1998). In addition to its well-known chaperoning machinery, it is also important for activity of reverse transcriptase of hepatitis B virus and NS2/3 protease of hepatitis C virus (Hu and Seeger 1996; Hu et al. 1997; Hu and Anselmo 2000; Waxman et al. 2001). Furthermore, HSP90 is required for the proper localization of DNA polymerase of herpes simplex virus (Burch and Weller 2005) and intracellular transportation of the RNA polymerase of influenza virus (Naito et al. 2007) and viral capsids in early hepatitis E virus infection (Zheng et al. 2010). HSP90 has been found to be a part of receptor complex in dengue virus entry (Reyes-del Valle et al. 2005). Moreover, HSP90 participates in the replication cycle of multiple other virus families such as Bimaviridae (Lin et al. 2007), Filoviridae (Smith et al. 2010), Polyomaviridae (Miyata and Yahara 2000) and Togaviridae (Rathore et al. 2014). A recent large-scale transcriptomics profiling of cells infected with SARS-CoV-2 identified HSP90 as important for infection. Inhibition of HSP90 activity caused reduction in viral replication and proinflammatory response (Li et al. 2020; Wyler et al. 2021). In Avibirnavirus infection, HSP90AA1 triggers autophagy by AKT-mTOR-dependent pathway upon pathogen recognition which is a crucial step in controlling the pathogenesis (Hu et al. 2015). The HSP90AA1 machinery is involved in maintaining stability of rabies virus phosphoprotein (Xu et al. 2016). The ER-predominant HSP90B1 is also released in extracellular space and is taken up by antigen-presenting cells (APCs) in case of vaccinia virus–induced cell lysis (Berwin et al. 2001). This isoform is critical in antigen cross-presentation in long-lived lymphocytic choriomeningitis virus infection (Basta et al. 2005). Inhibition of HSP90B1 also inhibits replication of flaviviruses including dengue virus and Zika virus (Rothan et al. 2019). HSP90 has been also reported as a possible anti-viral target in a number of studies (Wang et al. 2017).

Considering the diverse range of cellular function of HSP90, we still have limited knowledge on its role in the area of HIV research. HSP90 has been reported to positively regulate HIV-1 gene expression in acutely infected cells and localize on the viral promoter which might directly control viral transcription (Vozzolo et al. 2010). Another study has shown that the phenomenon of HSP90 co-localization with actively transcribing provirus is enhanced in hyperthermic conditions leading to increase in HIV-1 replication (Roesch et al. 2012). Recently, we have reported that the LTR-driven gene expression is enhanced and suppressed by over-expression and silencing of HSP90 respectively in HEK293T cells and novel HSP90 inhibitors can suppress virus replication, indicating its possible use as a therapeutic target (Trivedi et al. 2019). Like other elements of heat shock pathway namely heat shock factor-1 (HSF-1), HSP90 also governs HIV-1 reactivation from latent reservoirs present in resting host cells (Timmons et al. 2020). HSP90 regulates NF-κB pathway that connects T-cell activation with viral replication, thereby contributing to proviral reactivation (Anderson et al. 2014). Quiescence induced by inhibition of HSP90 in human hematopoietic stem and progenitor cells (HSPCs) makes them susceptible to predominantly latent HIV-1 infection (Painter et al. 2017). By proteasome inhibition, HSP90 facilitates the latent reactivation process by maintaining positive transcription elongation factor b (p-TEFb) functional, which in turn indicates the role of HSP90 in viral transcriptional elongation (Pan et al. 2016). In primary T cells, inhibition of HSP90 blocks p-TEFb assembly which suppresses the reactivation from HIV-1 latency (Mbonye et al. 2018). Another study has also shown that pan-histone deacetylase inhibitors (HDIs) are less effective than the class 1-selective HDIs in mediating viral reactivation due to more off-target inhibition of cellular factors like HSP90 which are crucial for optimal HIV transcription (Zaikos et al. 2018). HSP90AA1 is reportedly involved in HIV-1 reactivation and has also been predicted to play an important role in HIV-associated encephalitis pathogenesis (Shityakov et al. 2015). In addition to its role in HIV-1 replication and reactivation, HSP90 contributes to the infectivity of progeny virus. The cytosolic isoform HSP90AB1 can rescue infectivity of ritonavir-resistant virus particles impaired by accumulation of the capsid-spacer peptide 1 (CA-SP1) precursor in HIV-1 (Joshi and Stoddart 2011). The same group further showed that HSP90AB1 is also present in virions outside the core and restores infectivity of HIV-1 particles with mutated capsid proteins (Joshi et al. 2013). Since viral antigens bound to HSPs are known to augment antiviral immunity, few studies have demonstrated how HSP90B1 can be used as an adjuvant to enhance cellular and humoral immune responses against HIV-1 infection (Gong et al. 2009; Kadkhodayan et al. 2017). Knockdown of HSP90B1 also causes a significant increase in expression of the CD4 receptor in HIV-1-infected SupT1 T-cells (Landi et al. 2014). Based on all of the above,

one can speculate that it will be interesting to elucidate the role of non-cytosolic HSP90 isoforms in virus infection.

HSPH family (HSPH 110)

The literature on the HSP110 (also termed as HSP105) family is the most limited. HSP110 is part of the HSP70 superfamily. It is related to the HSP70 family, but its ATPase domain is more divergent and the C-terminal domain is of varying lengths. There is also the presence of a long loop-like structure between the β sandwich subdomain and the α helical subdomain (Lee-Yoon et al. 1995; Easton et al. 2000) (Fig. 2f). The HSP110 family is the third most abundant heat shock protein family. In heat shocked CHO cells, HSP110 forms 0.7% of the total cellular proteins (Subjeck et al. 1982). The family consists of isoforms other than HSPH1 (HSP105, HSP110) as well. The 170-kDa glucose regulatory protein HSPH4 (GRP170) is a related member that resides in the endoplasmic reticulum of the cell. It consists of an ATP-binding domain and an NDEL sequence in the carboxy-terminal domain (Chen et al. 1996). Another isoform is HSPH3 (APG1), an isoform that is expressed constitutively in testis germ cells (Kaneko et al. 1997). Yet another isoform that comes under the HSP110 family is HSPH2 (APG2), which seems to be required for cytoplasm to vacuole targeting, autophagy and pexophagy pathways (Wang et al. 2001a). The genes of both human HSPH2 and HSPH3 were cloned from a human testis cDNA library. In human endothelial cells, APG1 transcripts and not APG2 transcripts was induced by a rise in temperature from 32 °C temperature to 39 °C (Nonoguchi et al. 1999).

The HSP110 family also acts as nucleotide exchange factors for the HSP70 family. It was first shown that the yeast HSP110, Sse1, interacts with the yeast HSP70 chaperones, Ssa and Ssb (Shaner et al. 2005). Using the yeast homologue, Polier et al. provided a structural basis of the nucleotide exchange on HSP70 catalyzed by HSP110, thereby releasing the bound ADP after one cycle of HSP70-driven ATP hydrolysis (Polier et al. 2008). Thus, it performs the role of molecular chaperone. Apart from its chaperone role, HSP110 is widely studied for its other roles in the cell. HSP110 has been investigated as a potential vaccine candidate in the phase I trial for cancer therapeutics as it was shown to induce the tumour-specific cytotoxic T lymphocyte response (Wang et al. 2001b; Shimizu et al. 2019). Overexpression of HSP110 (APG2 or HSPH2) may also correspond to earlier recurrence of cancer (Yang et al. 2015). HSP110 is also documented to have a critical role on the cardio-vascular system where it associates with endothelial nitric oxide synthase and induces dilations of the blood vessels (Benjamin and McMillan 1998). Recently, it was also demonstrated that upon genotoxic stress conditions, HSP110 translocates into the nucleus and induces the repair of damaged DNA both in vitro as well as in vivo (Causse et al. 2019). Additionally, HSP110 is crucial for spindle assembly checkpoint activation in case of heat shock–induced cell cycle arrest (Kakihana et al. 2019). Further, HSP110 is also shown to reduce the aggregation of alpha-synuclein and has positive impact on Parkinson's disease (Taguchi et al. 2019).

In case of virus infection, unlike other HSPs, the detailed role of HSP110 is yet to be characterized. However, few studies have shown significant modulation of HSP110 and its consequences on virus infection and host immune response. In case of flavivirus infections, HSP110 induces the virus-specific T-cell response in vitro; however, this enhancement is not observed in case of in vivo studies (McLaughlin et al. 2011). A critical step in the SV40 infection cycle is the penetration by the non-enveloped virus of the endoplasmic reticulum membrane to reach the cytosol. HSPH1 (HSP105) enables this by interacting with the ER DNAJB14 and cooperating with HSPA8 (Ravindran et al. 2015). A direct role for the other isoform of the HSP110 family, HSPH2 (APG2) in viral infections has not yet been delineated. However, a recent paper showed that APG2 shows up in a network of proteins connected to ACE2, a protein that is seemingly important for the SARS-CoV-2 virus entry. This is important because APG2 is a target for several drugs (Cava et al. 2020). HSPH2 (APG2) and not HSPH3 (APG1) is upregulated in Hepatitis B virus–related early stage hepatocellular carcinoma. HSPH3 (APG1/HSPA4L), on the other hand, is modulated by the Spanish flu virus that caused the 1918 pandemic as well as by the reassortant viruses of the 1918 influenza virus and human H1N1 virus (Watanabe et al. 2013). HSPH4 (GRP170) was shown to associate with viral interleukin-6 (vIL-6), encoded by human herpes virus (Giffin et al. 2014). In another instance, Khachatoorian et al. reviewed several studies documenting the increase in the expression of HSP110 upon Hepatitis C virus (HCV) infection (Khachatoorian and French 2016). Although substantial evidences indicate the role of HSP110 in association with HSP40 and HSP70, the direct role of HSP110 is yet to be elucidated in case of HIV and other virus infections.

Conclusion and future perspectives

The review highlights the presence of both highly diverse and conserved heat shock proteins (HSPs) inside the cells that help to maintain a general cellular homeostasis, and are also modulated during stress conditions. These proteins are classified into various families based on their molecular weights. Furthermore, present literature shows that each family comprises several isoforms. These proteins are widely distributed throughout the cellular compartments such as the cytoplasm, nucleus, endoplasmic reticulum and mitochondria, and some

of the isoforms are compartment specific; for example, TRAP1 of the HSP90 family is located primarily in the mitochondria as is HSPA9 of the HSP70 family. The presence, diversity and localization of these isoforms suggest specific roles for them. Roles for some of these isoforms have been delineated in cancer, viral infection and other diseases, but a lot of it still remains to be elucidated.

With limited resources, viruses are unable to infect, propagate and produce functional virus progeny in the host on their own. Thus, viruses hijack the cellular machinery that also enables them to evade from the host immune response. In case of HIV-1, viral replication, the latency and reactivation of latent provirus is largely regulated by a variety of host factors. Cellular heat shock family proteins have been identified as the host proteins with plethora of functions in case of HIV infection and pathogenesis. However, an elaborate study on the isoform-specific role of HSPs in case of HIV and other virus infections is yet to be elucidated, although progress has been made on some fronts as highlighted in this review. In case of sHSPs, out of 10 isoforms, only 4 are characterized to a limited extent in HIV-1 infection. Similar gaps exist in the studies on the role of CCT. While different subunits of the CCT complex have been reported to participate in other virus life cycles, there is only limited information on their role during HIV infection. The literature on HSP40 also presents the same lacunae. The family's highly diverse nature is indicative of specialized functions possibly in both cellular homeostasis and disease conditions. Further investigations will have to be carried out to understand the specific roles of each of the isoform in HIV-1 infection. The current pandemic caused due to SARS-CoV-2 has further highlighted the importance of HSPs in viral infections. For example, chaperones such as HSP60, HSP70 and HSP90 are immunogenically similar to certain SARS-CoV-2 proteins, leading to cases of molecular

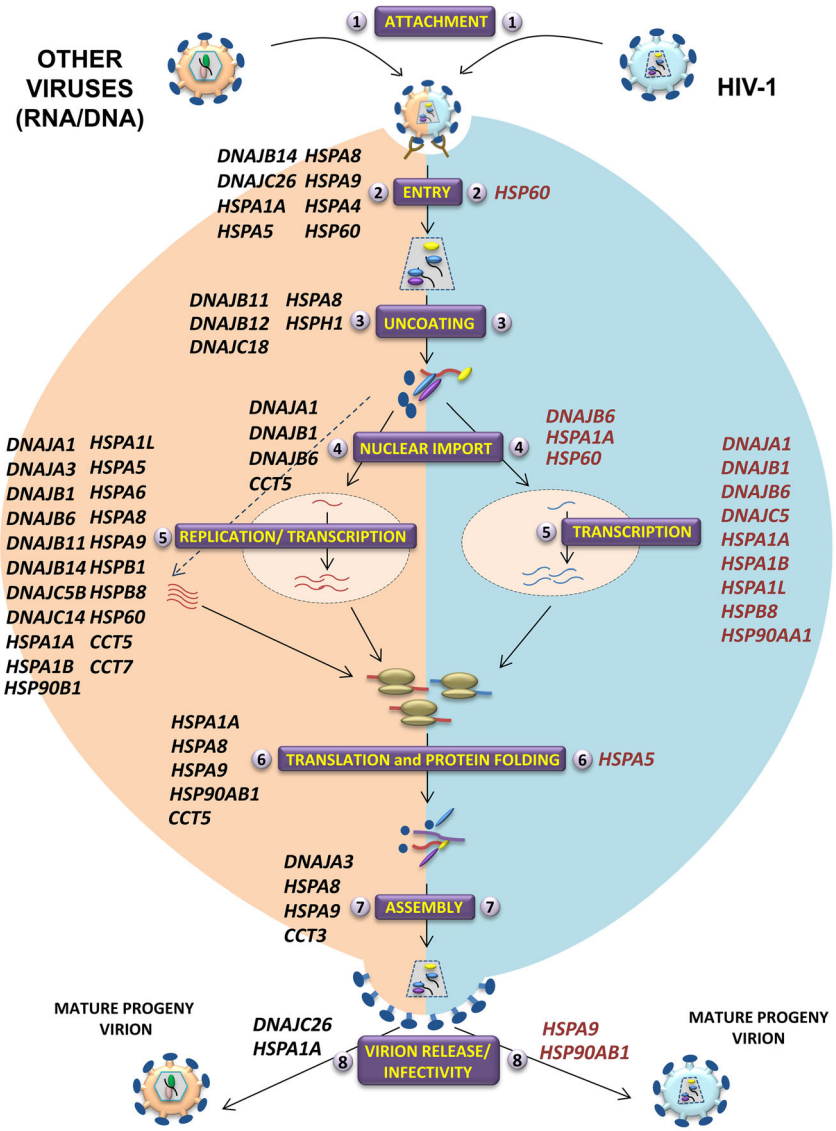

Fig. 3 Involvement of various isoforms of HSPs at different stages of the life cycle of RNA/DNA viruses (left half) and HIV-1 (right half). Upon literature search, several HSP family members have been identified that participate in positive or negative regulation of different stages of the life cycle of various viruses. In this graphical presentation, the members of different HSP families are presented at different stages of the virus life cycle labelled as (1) attachment, (2) entry, (3) uncoating, (4) nuclear import, (5) replication or transcription, (6) translation and protein folding, (7) assembly and (8) virion release. This comparative presentation indicates isoforms reported to be involved in other virus' life cycle and in HIV-1 infection

mimicry. Cross-reactive antibodies produced after infection can cause the body to attack self, leading to some of the pathological manifestations seen in COVID-19 (Paladino et al. 2020; Kasperkiewicz 2021). Figure 3 shows that while more studies have been performed in understanding the role of various isoforms in different steps of the life cycle of other viruses, much remains to be studied and elucidated in case of HIV-1 infection. Furthermore, these studies may enable us to develop specific therapeutic strategies to control the virus spread and AIDS pathogenesis. Thus, it becomes imperative to study and understand the role of specific HSP isoforms and their interaction with other proteins during different stress conditions including virus infection.

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Declarations

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