



Heat Shock Protein 60 in Hepatocellular Carcinoma: Insights and Perspectives

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Heat shock protein 60 (HSP60) is a mitochondrial chaperone that is implicated in physiological and pathological processes. For instance, it contributes to protein folding and stability, translocation of mitochondrial proteins, and apoptosis. Variations in the expression levels of HSP60 have been correlated to various diseases and cancers, including hepatocellular carcinoma (HCC). Unlike other HSPs which clearly increase in some cancers, data about HSP60 levels in HCC are controversial and difficult to interpret. In the current review, we summarize and simplify the current knowledge about the role of HSP60 in HCC. In addition, we highlight the possibility of its targeting, using chemical compounds and/or genetic tools for treatment of HCC.

Keywords: heat shock proteins, hepatocellular carcinoma, cancer therapy, chaperones, therapeutic resistance, chaperonin

INTRODUCTION

Hepatocellular carcinoma (HCC) is a common cancer of the liver with worldwide incidence and high mortalities. According to 2018 statistics, HCC is estimated to be the sixth frequently diagnosed cancer and the fourth main cause of death globally (Bray et al., 2018). Notably, the morbidity and mortality rates in men are two–threefold greater than in women. Moreover, HCC represents the most common cancer in 13 geographically diverse nations including countries from Africa like Egypt, Gambia, and Guinea as well as countries from Eastern and South-Eastern Asia such as Mongolia, Cambodia, and Vietnam. Some reports highlight the spread of the disease among developed countries despite the advances in vaccine development (Stasi et al., 2016; Ghouri et al., 2017). Several risk factors lead to HCC development and contribute to its complex pathogenesis such as chronic viral infections including hepatitis B virus (HBV) and hepatitis C virus (HCV), alcoholic cirrhosis, non-alcoholic steatohepatitis (NASH), exposure to chemical carcinogens, and ingestion of aflatoxin-contaminated foods (Fujiwara et al., 2018) (**Figure 1**).

Heat shock proteins (HSPs) are a set of evolutionarily conserved molecules which exist in almost all living organisms (Lindquist and Craig, 1988; Jäättelä, 1999; Sørensen et al., 2003; Chen et al., 2018). Generally, these numerous proteins are classified into families and subfamilies of distinct molecular masses that range from about 10 to 110 kDa. The families of HSPs are grouped into large HSPs such as HSP110 and glucose-regulated protein 170 (GRP170), small HSPs (sHSPs) besides HSP40 (DNAJ), chaperonin, or heat shock protein 60 (HSP60), HSP70, and HSP90 (Kampinga et al., 2009; Chatterjee and Burns, 2017). Members of HSPs are commonly known to function as molecular chaperones assisting in the folding of newly synthesized as well as misfolded proteins.

In addition, they are involved in the elimination of terminally misfolded proteins through their targeting to cellular proteolytic machineries (Hartl et al., 2011; Hipp et al., 2019).

HSP60 (also called Cpn60) is a ubiquitous chaperone present in all mammalian cells and tissues including liver. This HSP performs many physiological functions that are not restricted to its cellular canonical location in the mitochondria (Gupta et al., 2008; Merendino et al., 2010). It supports mitochondrial protein folding and assists in proteolytic degradation of denatured or aberrantly folded proteins in an ATP-dependent fashion (Azem et al., 1995; Henderson et al., 2013). HSP plays numerous physiological roles but can also be pathogenic in various conditions, including cancer and neurodegenerative diseases (Cappello et al., 2008; Bross et al., 2012; Zhou et al., 2018). Recent reports highlight the role and implication of HSP60 in human cancer development and management whereby its targeting has revealed promising therapeutic outcomes (Pace et al., 2013; Li et al., 2014; Meng et al., 2018).

HSP60 has been studied as biomarker for diagnosis and prognosis assessment and as therapeutic agent in a range of diseases, such as gastric (Li et al., 2014), bronchial (Cappello et al., 2005), colorectal (Hamelin et al., 2011) and ovarian cancer (Guo et al., 2019), as well as glioblastoma (Khalil and James, 2007) and esophageal squamous cell carcinoma (Faried et al., 2004). Nevertheless, the role of HSP60 in HCC remains poorly understood. In the current review, we discuss the oncogenic role of HSP60 and its potential as therapeutic target, focusing on HCC. Moreover, we shed the light on the potential of HSP60 targeting as a therapeutic strategy to combat HCC.

STRUCTURAL AND ORGANIZATIONAL ASPECTS OF HUMAN HSP60

Generally, the term HSP60 refers to the mtHSP60 while the cytosolic homolog is known as TRiC/CCT. There is a notion that mtHSP60 arose from bacterial ancestors that were engulfed by early eukaryotic cells to produce the mitochondrial organelle (Hemmingsen et al., 1988). Mechanistically, HSP60 (HSPD1) forms tetradecamers consisting of two stacked heptameric rings with a central cavity that harbors the client protein. Importantly, HSPE1 (the homolog of bacterial GroES and known as HSP10) forms a single heptameric ring that functions as a cap for the HSPD1 assembly. This structural organization is essential for the ATP-dependent functionality of HSP60 in protein folding (Pace et al., 2013; Nisemblat et al., 2015; Okamoto et al., 2015). On the other hand, the cytosolic TRiC/CCT consists of eight subunits encoded by *TCPI* and *CCT2-8* genes and has its own built-in cap system (Leitner et al., 2012). In human, HSP60 is encoded by a gene located on chromosome 2q33.1 (Hansen et al., 2003). hHSP60 resides mostly in the mitochondrial matrix and the outer mitochondrial membrane with potential localization to other extra-mitochondrial sites (Soltys and Gupta, 1999; Gupta et al., 2008). Despite its constitutive expression under physiological conditions, increased

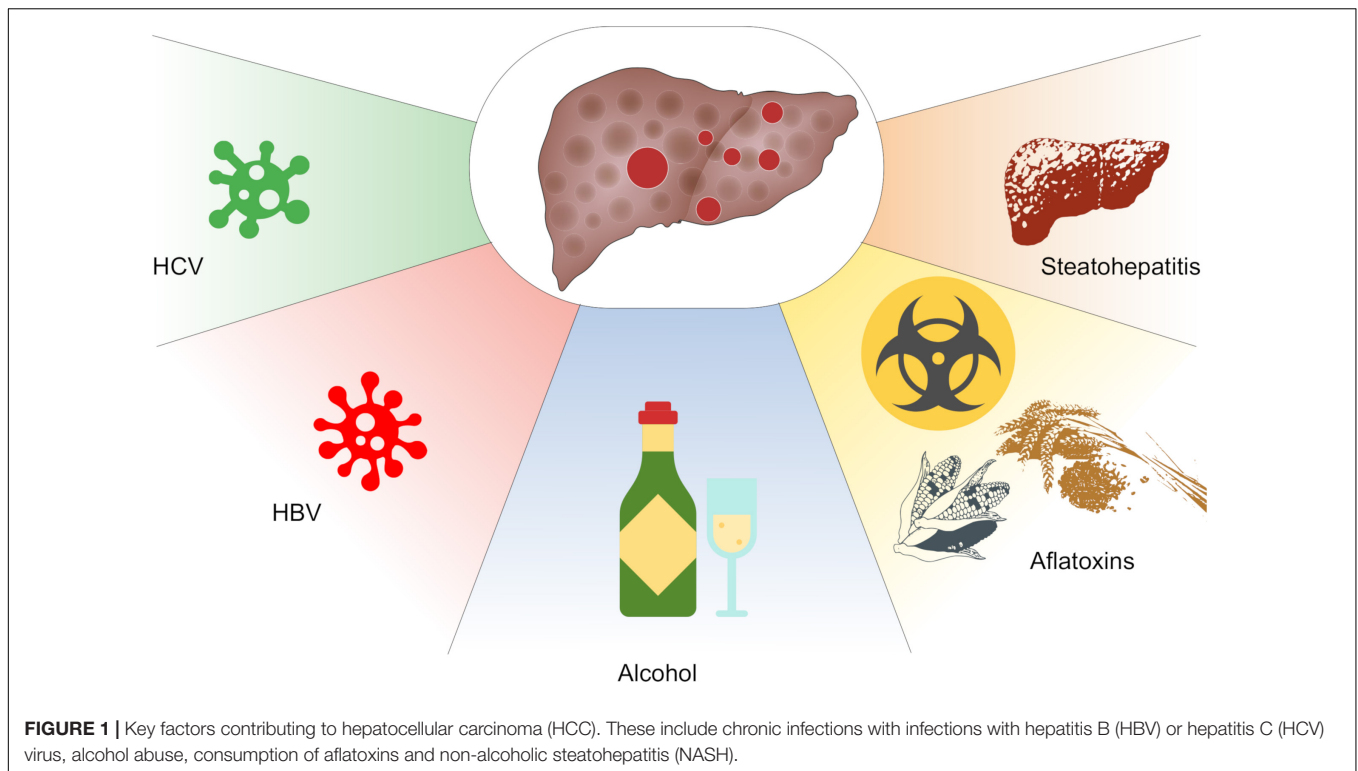
levels of HSP60 can be induced following mitochondrial damage or heat stress.

In this manuscript, we use the word expression and its derivatives to indicate presence or quantitative changes of any protein, e.g., Hsp60, indiscriminately, without considering the cause, namely whether they are due to changes in the levels of expression of the pertinent gene, or to post-transcriptional or post-translational mechanisms, or a combination of them. Like most HSPs, hHSP60 is regulated via heat shock response by binding of the heat shock element (HSE) to the specific region on the DNA (Hansen et al., 2003). It should be noted that increasing reports correlate the variant expression of hHSP60 in different cellular compartments as well as biological fluids, including blood and cerebrospinal fluid, to human pathological conditions (Deocarlis et al., 2006). Hence, detection and quantitative determination of HSP60 alterations may provide clues for studying disease mechanisms, prognosis, and treatment progress (Nakamura and Minegishi, 2013).

THE ANTI-APOPTOTIC AND ONCOGENIC ROLES OF HSP60

An interesting activity of HSP60 in mammalian cells is its contribution to apoptosis regulation. Early studies in the leukemic Jurkat T cell line revealed that HSP60 and its associated chaperone HSP10 form a complex with caspase-3 leading to its maturation. This observation suggested a potential chaperoning activity of HSP60 toward caspase-3 (Samali et al., 1999; Xanthoudakis et al., 1999). In addition, other studies showed that HSP60 was expressed on the surface of murine lymphoma cells (Sapozhnikov et al., 1999). Moreover, HSP60 has been linked to tumor cell apoptosis in a process that involves increased surface expression of HSP60 and subsequent stimulation of anti-tumor immune responses (Feng et al., 2001). On the other hand, increased expression of HSP60 in cardiac myocytes has been found to inhibit apoptosis indicating a significant yet complex role of HSP60 in the apoptotic machinery of tumor cells (Henderson et al., 2013). These findings in tumor and non-tumor cells raised many questions whether HSP60 is an anti- or pro-apoptotic protein (Henderson et al., 2013). Importantly, the previous study that included many *in vitro* apoptotic systems could unravel some mechanistic lines of HSP60 apoptotic action (Chandra et al., 2007). One significant conclusion was that the cytosolic accumulation of HSP60 is a common process during apoptosis regardless of its mitochondrial release and its pro-survival or pro-apoptotic behavior involves differential interactions with caspase-3 (Chandra et al., 2007).

Owing to its anti-apoptotic properties, it is not surprising that HSP60 displays tumorigenic functions. HSP60 supports cancer development via increasing tumor growth, promoting angiogenesis and metastasis, reducing mitochondrial permeability transition, and counteracting apoptosis (Wu et al., 2017). In accordance with these functions, secretion of HSP60 has been described in all investigated tumor cells suggesting a role in tumor growth and dissemination, where the secretion process was independent of cell death (Merendino



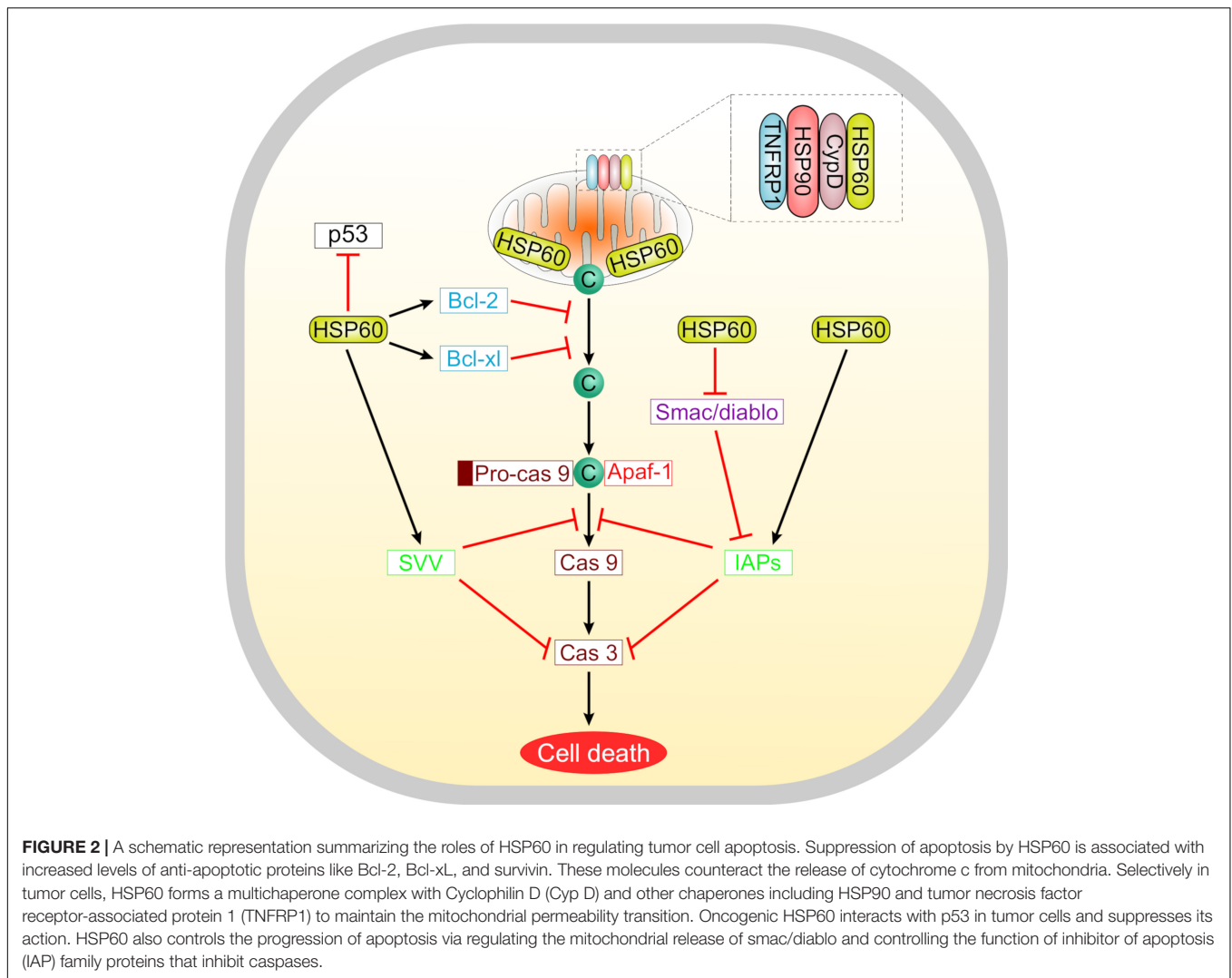
et al., 2010). Further molecular investigations revealed that pro-carcinogenic effects of HSP60 are due to its ability to enhance cancer cell survival via interacting with and inhibiting the intracellular isoform of clusterin in neuroblastoma cells (Chaiwatanasirikul and Sala, 2011).

Suppression of apoptosis by HSP60 is concomitant with overexpression of the anti-apoptotic proteins Bcl-2, Bcl-xL, and survivin, maintenance of the mitochondrial transmembrane potential, and inhibition of caspase 3 activation (Deocaris et al., 2006). Cytosolic HSP60 inhibits the translocation of the pro-apoptotic protein Bax into the mitochondria, hence promoting cell survival (Xanthoudakis et al., 1999; Lianos et al., 2015). Furthermore, the anti-apoptotic actions of HSP60 involve its interaction with several molecules including the mitochondrial HSP70, survivin, and p53. HSP60 is also a potent regulator of the mitochondrial permeability transition which is mediated through a multichaperone complex comprising HSP60, HSP90, and tumor necrosis factor receptor-associated protein-1 (TNFRP1), particularly assembled in tumors but not in normal cells (Ghosh et al., 2010; Rodríguez et al., 2016) (**Figure 2**). In tumor cells, the anti-apoptotic HSP60 has been found to interact with cyclophilin D in the mitochondrial permeability transition pore where subsequent disruption of this interaction altered the mitochondrial permeability transition, stimulated caspase-dependent apoptosis, and led to suppression of tumor cell growth (Ghosh et al., 2010).

Interestingly, inhibition of HSP60 could enhance the tumor suppressive activity of insulin-like growth factor binding protein 7 (IGFBP7) in colorectal cancer cells (Ruan et al., 2010). In

human cancer HeLa cells, cytosolic HSP60 has been shown to support nuclear factor- κ B (NF- κ B)-dependent survival through binding and regulating the activity of I κ B kinase (IKK) (Chun et al., 2010). Moreover, HSP60 knockdown in ovarian cancer cells inhibits tumor progression by breaking mitochondrial proteostasis, and inactivating the mTOR pathway (Guo et al., 2019). With regard to cancer metastasis, HSP60 has been described as a key chaperone that promotes metastatic phenotypes both *in vitro* and *in vivo* (Tsai et al., 2009). This effect is attributed to a significant interaction between HSP60 and β -catenin resulting in overexpression of β -catenin and enhancement of its transcriptional activity (Tsai et al., 2009).

Upregulation of HSP60 has been implicated in cervical cancer progression and prognosis (Hwang et al., 2009). Likewise, expression of HSP60 has been linked to the progression of prostate cancer (Castilla et al., 2010; Hoter et al., 2019). In ovarian cancer, the HSP60 transcript levels were variable in cancerous tissues. However, several reports linked high HSP60 expression to advanced ovarian cancer stages highlighting its prognostic value (Kimura et al., 1993; Hjerpe et al., 2013; Hoter and Naim, 2019). In breast cancer, autoantibodies against HSP60 have been reported to be elevated and their levels were remarkably associated with cancer grade (Hamrita et al., 2008). Sera obtained from patients with colorectal cancer showed increased concentrations of HSP60 that were associated with advanced stages of colorectal cancer (Hamelin et al., 2011). These findings strengthen the notion of utilizing HSP60 as a diagnostic and prognostic marker in several types of cancers.



HSP60 IS A KEY PLAYER IN MAJOR ETIOLOGIES OF HCC

In-depth analyses of the etiologies leading to HCC reveal that HSP60 plays a yet unclear role in diverse causalities of HCC development. HSP60 is implicated in the predisposing factors of HCC including HBV, HCV, and alcoholic hepatitis as described in the next section.

HSP60 IN HEPATITIS B VIRUS (HBV) INFECTION

HBV infection is a major risk factor for the development of HCC worldwide. Chronic infection with HBV predisposes patients with cirrhotic liver or those devoid of hepatic cirrhotic lesions to HCC (Xu et al., 2014). Notably, the central burden of the HCC (85%) is noticed in the HBV endemic regions (Niu and Hann, 2017). Initial studies demonstrated that HSP60 interacts with human HBV polymerase leading to its maturation into its

active form (Park and Jung, 2001; Park et al., 2002). Moreover, other studies showed that the transcriptional transactivating protein HBx of HBV form a complex with HSP60 and HSP70 suggesting their contribution to virus-mediated liver oncogenesis (Zhang et al., 2005). In line with previous findings, comparative proteomic analysis of liver HepG2.2.15 cell line revealed that HSP60 forms, together with HSP70 and HSP90, a chaperone complex that is suggested to influence HBV production and secretion (Liu et al., 2009). Furthermore, targeted therapy toward HSP60 using antisense oligonucleotide greatly interferes with HBV replication (Park et al., 2003).

HSP60 IN HEPATITIS C VIRUS (HCV) INFECTION

Similar to its role in HBV infection, HSP60 has been found to mediate HCV infection in several aspects. HSP60 has been demonstrated to interact with the N-terminal domain of the core structural protein of HCV which is involved in HCV

chronic infection-associated liver diseases (Kang et al., 2009). The HSP60–HCV interaction has been found to mediate the production of reactive oxygen species (ROS) and regulate apoptosis. Moreover, high expression of HSP60 in human liver cells expressing the HCV core protein could protect against TNF- α induced cell lethality via reduction of ROS production (Kang et al., 2009).

HSP60 IN ALCOHOLIC HEPATITIS

Initial studies showed that HSP60 levels were increased in liver tissues of patients with acute alcoholic liver. Additionally, raised circulating anti-HSP60 IgA levels have been reported. These findings suggest that overall upregulation of HSP60 in tissues and serum might be one of the pathogenic mechanisms leading to the development and progression of liver damage in alcoholic hepatitis (Koskinas et al., 1993). In accordance with these results, other research groups reported a strong association between IgA levels against HSP60 and patients with acute alcoholic hepatitis (Winrow et al., 1994).

HSP60 IN HCC

Early studies showed that the expression of HSP60 was highly increased in chronic active hepatitis with preferential accumulation in areas of inflammatory infiltrates (Lohse et al., 1993). Several proteomic and immunohistochemical analyses revealed upregulation of a multitude of chaperones including HSP60 in HCC (Lim et al., 2002, 2005; Kim et al., 2003). Recent reports showed that both blood and urine mRNA levels of HSP60 were significantly higher in HCC post-HCV patients compared with those having cirrhosis or healthy controls (Abd El-Salam et al., 2017). Moreover, proteomic analysis of HCC tumor associated antigens has identified HSP60 as an important HCC marker. Further serological investigations revealed that HSP60 could be detected not only in sera of HCC patients but also in patients with chronic hepatitis and liver cirrhosis (Looi et al., 2008). With reference to recent meta-analysis performed on patients with digestive cancers, HSP60 has been considered an advanced biomarker for HCC (Chen et al., 2019).

Molecular studies revealed that the redox status of HSP60 is crucial in the hepatocyte growth factor (HGF)-induced ERK phosphorylation and HepG2 cell migration (Lin et al., 2016). Interestingly, there are discrepancies among the recent studies concerning the expression levels and molecular roles of HSP60 in HCC. For instance, one study reported a reduction in HSP60 expression levels in HCC tissues compared to the peritumor tissues (Zhang et al., 2016). Further analyses performed by this group revealed that lowered HSP60 levels were significantly linked to the tumor differentiation grade whereby downregulation of HSP60 was associated with poor prognosis. Additionally, increased HSP60 expression cancer/pericancer (C/P) ratio was associated with enhanced overall survival as confirmed in a cohort study of 107 HCC

patients (Zhang et al., 2016). At the molecular level, HSP60 was found to stimulate the differentiation of BEL-7402 and SMMC7721 and inhibit the invasion of BEL-7402 and SK-Hep-1 HCC cell lines. Furthermore, *in vivo* experiments have proven that ectopic expression of HSP60 exerts significant anti-metastatic activity following inoculation into hepatic tissue of nude mice (Zhang et al., 2016). Another biological function reported was that overexpression of HSP60 has been associated with mitochondrial biogenesis as confirmed by its direct correlation to the levels of mitochondrial biogenesis markers cytochrome c oxidase subunit (COX4) and mitochondrial DNA (mtDNA) (Zhang et al., 2016). These findings are in contrast with those obtained by another group as summarized in **Table 1** (Huang et al., 2018).

TARGETING HSP60 IN HCC

Recent reports highlight the perspectives of targeting HSP60 as a future tool for cancer treatment (Nakamura and Minegishi, 2013; Cappello et al., 2014; Meng et al., 2018). In fact, HSP60 inhibition has been implemented as a therapeutic strategy in various types of cancers including melanoma (Kamm et al., 2019), pancreatic cancer (Zhou et al., 2018), and ovarian cancer (Guo et al., 2019). However, few reports concerned its targeting in HCC. Although one previous study (Zhang et al., 2016), discussed in the previous section, reported contradicting roles for HSP60 in terms of apoptosis and proliferation to what is commonly known about this chaperone in most cancer types, different findings have been reported (Huang et al., 2018) (**Table 1**). In experiments aiming at elucidating the potential of HSP60 inhibition for HCC treatment, this group has revealed significant enhancement of cell apoptosis, reduction of cell proliferation, and downregulation of survivin upon silencing of HSP60 in two HCC cell lines (Huang et al., 2018). Interestingly, these apoptotic and anti-proliferative effects were minimal or neglected in HSP60-silenced healthy hepatocytes (Huang et al., 2018). In line with these *in vitro* experiments, suppression of HSP60 in hepatoma xenograft mice models using jet polyethylenimine mediated shHSP60 delivery systems (PEI/shHSP60 complexes) resulted in significant reduction of tumor volumes and weights in the shHSP60 group compared to the control group (Huang et al., 2018). On the other hand, the clinical outcomes relative to HSP60 expression were different in the respective investigating groups. While one group showed a correlation between Hsp60 expression and clinico-pathological characteristics of HCC patients, the other group revealed no significant correlation. Their conclusion was attributed to relative high expression of HSP60 in both cancerous and corresponding non-cancerous hepatic tissues in HCC patients.

INHIBITORS OF HSP60

Compared with other HSPs such as HSP90 and HSP70, few compounds have been known to target HSP60 in the oncology

field (Nakamura and Minegishi, 2013). Recent reports have shed the light on the potential HSP60 inhibitors and their usage for cancer therapeutic purposes (Meng et al., 2018). According to their mechanism of action, HSP60 inhibitors have been classified into type I inhibitors and type II inhibitors. Type I inhibitors act by blocking the ATP binding site of HSP60 and subsequently interfering with ATP hydrolysis and folding activities, whereas Type II compounds function through covalent interaction with specific cysteine residues within the HSP60 molecule. Nevertheless, full understanding of the exact mechanisms of HSP60 inhibitors is still lacking (Meng et al., 2018). **Table 2** provides an overview about the known HSP60

TABLE 1 | Highlights of the two contradicting studies concerning HSP60 roles in HCC.

HSP60 main function	HSP60 functions as tumor suppressor of HCC ^a	HSP60 supports the development and progression of HCC ^b
HSP60 levels	Both mRNA and protein levels are reduced in tumor tissues of HCC patients compared with peritumor tissues	In liver tissues of HCC patients, high levels of HSP60 were found in 56.6% of specimens compared to 40.0% with reduced HSP60 levels
Clinical correlation	HSP60 expression ratio in cancerous and pericancerous tissues of HCC patients [expressed as cancer/pericancer (C/P) ratio] is associated with overall survival. Low ratio is linked to poor overall survival and vice versa	No significant correlation between the quantitative variations of HSP60 expressed as paired tumor/non-tumor ratio (T/N) ratio and the clinical outcomes Only elevated HSP60 expression levels in non-cancerous tissues were associated with shorter overall survival. Moreover, there exists a positive correlation between HSP60 expression in non-cancerous tissues and macrovascular invasion, high tumor grades, and large tumor size
<i>In vivo</i> findings	Ectopic expression of Hsp60 in the left hepatic lobes of nude mice stimulated the differentiation and suppressed both intrahepatic and lung metastasis	Targeting HSP60 in mice xenograft models by jetPEI/HSP60-shRNA revealed significant reduction in both tumor size and weight compared to the control group
Molecular roles of HSP60 in HCC cells	HSP60 induced differentiation HSP60 inhibited invasion and metastasis HSP60 promotes mitochondrial biogenesis No effect on proliferation No effect on apoptosis	Its role in differentiation was not experimentally investigated Its role in metastasis was not experimentally investigated No significant alterations in mitochondrial mass upon HSP60-silencing in HCC cells HSP60 silencing resulted in marked suppression of cell growth and proliferation HSP60 silencing destabilized survivin and promoted cell death
Conclusion	Hsp60 exerts a tumor suppressor function, and might be utilized as a potential therapeutic target in the treatment of HCC	HSP60 can serve as prognostic marker as well as a therapeutic target for HCC

^{a,b}Studies performed by Zhang et al. (2016) and Huang et al. (2018), respectively.

TABLE 2 | Summary of known HSP60 inhibitors^a.

Class	Inhibitor	Effect	References
Natural products	Mizoribine	Binds to the HSP60 ATPase domain and inhibits the chaperoning activity of Hsp60-Hsp10 complex	Itoh et al., 1999; Tanabe et al., 2012
	Epolactaene	Inhibits the chaperone activity of HSP60 with yet unclear mechanism	Nagumo et al., 2005; Meng et al., 2018
	ETB (tert-butyl ester of epolactaene)	Interacts with Cys442 of HSP60 leading to potential allosteric modulation of the ATP binding pocket	Nagumo et al., 2005
	Myrtucommulone A (MC)	Interacts directly with HSP60 leading to aggregation and misfolding of cancer related proteins	Wiechmann et al., 2017
Synthetic compounds	Stephacidin B	Performs anticancer activities	Qian-Cutrone et al., 2002; Wulff et al., 2007
	Avrainvillamide	Anticancer activities	Fenical et al., 2000
	O-carboranylphenoxyacetanilide	Binds to HSP60 and inhibits the hypoxia-inducible factor (HIF) activation	Ban et al., 2010
	Gold (III) porphyrin complexes such as A prototype gold (III) complex [Au(TPP)Cl] (10)	Despite its poorly understood mechanisms, it suppresses HSP60 and performs significant anticancer activities	Lease et al., 2013; Teo et al., 2014; Hu et al., 2016

^aNakamura and Minegishi, 2013; Meng et al., 2018.

inhibitors which might be used in future HCC studies or combination therapies for cancer treatment.

CONCLUSION AND PERSPECTIVES

The enigma of HSP60 as a tumor suppressor or oncogenic molecule in HCC still exists. If we consider previous studies on the benefits of HSP60 targeting in variant cancer types such as in melanoma and ovarian cancer, we encourage further investigations aiming at finding ways to treat HCC by using drugs targeted at HSP60, to inhibit it if oncogenic or to potentiate it if anti-tumor. Since many HSP60 inhibitors are currently known and the list is still growing, several *in vitro* and *in vivo* studies are primarily and extensively needed to evaluate these inhibitors and their efficacy in HCC treatment regimens.

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AUTHOR CONTRIBUTIONS

AH, SR, and HN conceived the review topic. AH wrote the review draft and designed the figures. SR and HN edited and revised the review draft. All authors approved the final version of the review.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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