Acta virologica **62**: 33 – 40, 2018 doi:10.4149/av_2018_104

MINIREVIEW

Functional role of Hsp60 as a positive regulator of human viral infection progression

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Received April 25, 2017; revised July 24, 2017; accepted January 11, 2018

Summary. – Heat shock proteins (Hsps) are a family of proteins highly conserved in evolution. Members of the Hsp family are mainly responsible for proper protein folding, however they perform many other functions in living organisms. Hsp60 is a molecular chaperone that is present in mitochondria and cytosol of eukaryotic cells, as well as on their surface. It is also found in the extracellular space and in the peripheral blood. Apart from its role in assisting protein folding in cooperation with Hsp10, Hsp60 contributes to regulation of apoptosis, as well as participates in modulation of the immune system activity. Hsp60 may favor oncogenesis by promoting survival or growth of some tumor cell types. Hsp60 is a subject of medical research due to its role in pathogenesis of certain tumors and infectious diseases. In this review we discuss mechanisms by which Hsp60 promotes development and progression of infections caused by three human viruses: hepatitis B virus (HBV), human immunodeficiency virus (HIV) and influenza A virus.

Keywords: heat shock protein 60; Hsp60; viral infection; hepatitis B virus, human immunodeficiency virus; influenza A virus

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Abbreviations: Bcl-xL = B-cell lymphoma-extra large; DC = dendritic cell; HA = haemagglutinin; HBV = hepatitis B virus; HBV pol = HBV polymerase; HBx = HBV x protein; HIV = human immunodeficiency virus; Hsp = heat shock protein; IFN = interferon; MAVS = mitochondrial antiviral signaling protein; NA = neuraminidase; PB = polymerase basic protein; TLR = Toll-like receptor; Treg = regulatory T lymphocyte; vRNP = viral ribonucleoprotein

1. Introduction

Heat shock proteins (Hsps) are primarily known as molecular chaperones (David *et al.*, 2013). They are highly conserved in evolution due to importance of their functions in living cells (Jia *et al.*, 2011). Hsps and their homologues are widespread in nature and are present in both prokaryotic (Wood *et al.*, 2014) and eukaryotic (Stein *et al.*, 2014) organisms. These proteins are responsible for cell protection during stressful situations. Hsps are found in cells under normal conditions (Jia *et al.*, 2011), however their expression increases in reaction to intracellular and extracellular stress factors, such as high temperature, UV radiation, amino acids analogs, heavy metals, alcohols, reactive oxygen species (ROS), bacterial and viral infections and many other factors (Cymerys and Niemiałtowski, 2004; Resa-Infante *et*

al., 2011). The main function of Hsps is to maintain protein homeostasis in living cells. Molecular chaperones are responsible for correct folding of newly synthesized polypeptides (Parnas *et al.*, 2012) and allow denatured misfolded proteins to fold correctly (Wyżewski *et al.*, 2014). Moreover, Hsps are involved in many cellular processes, such as DNA synthesis, regulation of gene expression, cell differentiation and programmed cell death (Hwang *et al.*, 2009). Hsps also participate in intracellular cell signaling (David *et al.*, 2013).

Hsp60 is a chaperone protein with a molecular mass of 60 kDa. It occurs in the cytosol and mitochondria, as well as on the cell surface (Cappello *et al.*, 2008; Soltys and Gupta, 1996). It can also be released to the extracellular environment (Tian *et al.*, 2013). Hsp60 acts as molecular chaperone in cooperation with Hsp10 (Wyżewski *et al.*, 2014). In addition to assisting in the protein folding, Hsp60 regulates cell apoptosis and has both pro- (Gruber *et al.*, 2010) and anti- (Cohen-Sfady *et al.*, 2009; Ghosh *et al.*, 2008; Shan *et al.*, 2003) apoptotic activities. The latter may contribute to oncogenesis by enhancing survival or growth of certain tumor cell types (Schmitt *et al.*, 2007). Moreover, surface and extracellular soluble Hsp60 (sHsp60) are signaling molecules that affect immune cells and thus modulate immune activity of the host (Cappello *et al.*, 2008). It is suggested that surface Hsp60 activates antigen-specific cytotoxic T lymphocytes (CTLs), and is responsible for stimulation and maturation of dendritic cells (DCs) (Feng *et al.*, 2002). Extracellular Hsp60 is a ligand for certain surface receptors of immune cells, such as CD14, CD40 and Toll-like receptors (TLRs) (Pockley *et al.*, 2008; Tsan and Gao, 2004). It affects the cytokine secretion profile of antigen presenting cells (APCs) and regulates nitric oxide production by γδ T cells. Due to the ability to interact with various cell-surface receptors, extracellular Hsp60 can exert both pro- and anti-inflammatory effects (Cappello *et al.*, 2008).

Hsp60 is involved in pathogenesis of tumor and infectious diseases. In addition to its role in oncogenesis, Hsp60 may promote colonization of the host by different viruses (Cappello *et al.*, 2008). In this review we discuss mechanisms by which Hsp60 promotes infections by hepatitis B virus (HBV), human immunodeficiency virus (HIV) and influenza A virus.

2. Hsp60 in HBV infection

HBV belongs to the *Hepadnaviridae* family (Chen and Brown, 2012) and is a representative of the *Orthohepadnavirus* genus (He *et al.*, 2013). It is the etiological agent of chronic and acute hepatitis. HBV has small, partially double-stranded and partially single-stranded DNA genome (Minor and Slagle, 2014). The replication cycle of HBV and other hepadnaviruses includes synthesis of intermediate RNA called the pregenomic RNA (pgRNA) (Seeger and Mason, 2000). This structure serves as a template to form DNA in the process of reverse transcription (Minor and Slagle, 2014).

Hsp60 influences the course of HBV infection by interacting with viral proteins: HBV x protein (HBx) (Yasuo *et al.*, 2004) and HBV polymerase (HBV pol) (Park *et al.*, 2002). HBx is essential for viral infection and is involved in various interactions between the virus and the infected host cell. It influences host cell gene expression profile by acting as a transcriptional cofactor that binds basal transcriptional factors, such as p53 or RNA polymerase B 5 (RPB5) subunit of RNA polymerase. HBx affects many cellular signaling pathways and is involved in regulation of the cell apoptosis process. Studies on HBx demonstrate its contradictory effects in the regulation of apoptosis because it exhibits both pro- and anti-apoptotic activities in infected cells. HBx anti-apoptotic activity seems to contribute to hepatocarcinogenesis. On the other hand, there is evidence that HBx can facilitate apoptosis by regulation of the expression and sustainability of pro- and anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein family members (Zhang *et al.*, 2015). HBx up-regulates pro-apoptotic Bcl-2-associated x (Bax) protein expression (Liang *et al.*, 2007), as well as facilitates the anti-apoptotic myeloid cell leukemia-1 (Mcl-1) protein loss *via* caspase-3 cascade (Hu *et al.*, 2011). Moreover, HBx causes cytosolic calcium level increase that contributes to cell apoptosis through interacting with anti-apoptotic Bcl-2 and B-cell lymphoma-extra large (Bcl-xL) (Geng *et al.*, 2012). Studies show that mitochondrial Hsp60 (mtHsp60), as well as Hsp70 can bind HBx (Kim *et al.*, 2008; Murakami, 2001; Zhang *et al.*, 2000, 2015). The fragment of amino acid residues 88–117 of HBx is responsible for making a complex probably with the apical domain of endogenous mtHsp60. Hsp60, directly interacting with HBx, is essential for the activity of HBx and promotes HBx-induced apoptosis of infected host cell (Fig. 1) (Yasuo *et al.*, 2004).

Hsp60 also interacts with HBV pol, the multifunctional enzymatic viral protein. HBV pol plays a key role in several stages of viral replication. Acting as RNA-dependent DNA polymerase, HBV pol synthesizes plus-strand DNA on the viral pgRNA template. Then HBV pol synthesizes plus-strand DNA *via* its DNA-dependent DNA polymerase activity. HBV pol also acts as RNase H in the process of the pgRNA template degradation during minus-strand DNA synthesis. Moreover, HBV pol primes minus strand DNA synthesis from the tyrosine residue within amino-terminal domain of the enzyme polypeptide. HBV pol tyrosine residue provides a free hydroxyl group to form a phosphodiester bond with the first nucleotide of minus strand DNA (Beck and Nassal, 2007; Jones and Hu, 2013; Park *et al.*, 2002).

Hsp60 interacts with HBV pol and probably activates it; however exact mechanism of this interaction remains unclear (Park *et al.*, 2002). Hsp60 performs its chaperone function in

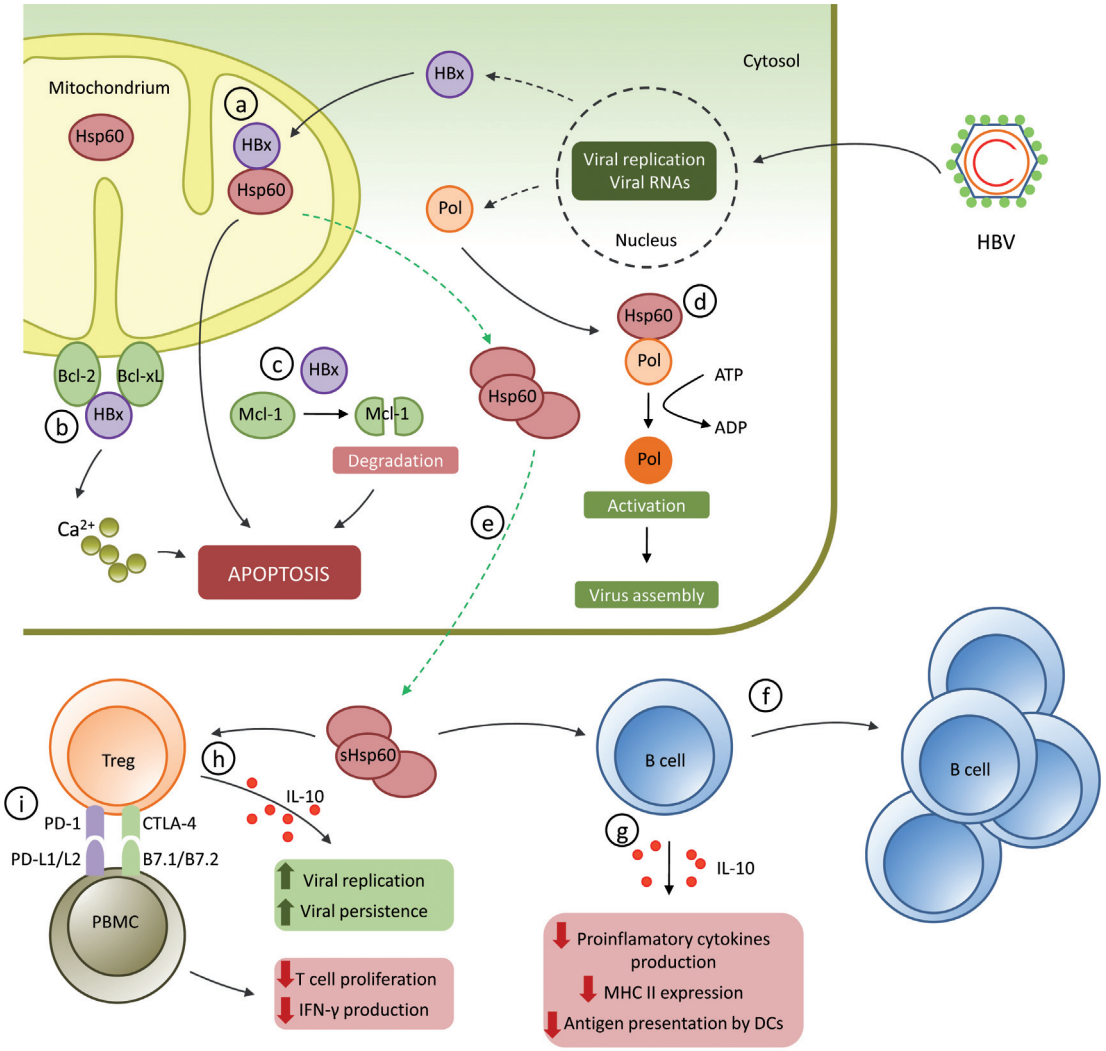

Fig. 1

Hsp60 influences the course of HBV infection by interacting with viral proteins: HBV x protein (HBx) and HBV polymerase (HBV pol)
(a) HBx is transported to the mitochondria where it binds to mitochondrial Hsp60. This interaction promotes HBx-induced apoptosis of the infected cell. HBx may also induce apoptosis through **(b)** interaction with anti-apoptotic B-cell lymphoma-2 (Bcl-2) and B-cell lymphoma-extra large (Bcl-xL) proteins and **(c)** degradation of myeloid cell leukemia-1 (Mcl-1) protein. **(d)** Hsp60 interacts with and activates HBV pol in an ATP dependent manner and promotes virus assembly. **(e)** HBV infection promotes secretion of Hsp60 from the infected cells. **(f)** Soluble Hsp60 (sHsp60) induces proliferation of B cells and **(g)** enhances production of IL-10 by B cells. IL-10 decreases production of proinflammatory cytokines, alters major histocompatibility complex (MHC) class II expression and antigen presentation by dendritic cells (DCs). **(h)** sHsp60 also enhances secretion of IL-10 by regulatory T lymphocytes (Tregs) promoting virus replication and persistence of HBV infection. **(i)** Tregs may inhibit activity of other cells *via* direct cell-cell contact through programmed death-1 (PD-1) and cytotoxic lymphocyte antigen-4 (CTLA-4) receptors. These interactions inhibit proliferation and production of interferon (IFN)-γ by T lymphocytes.

ATP dependent manner. ATP hydrolysis is necessary for the substrate protein release from the Hsp60 oligomer (Wyżewski *et al.*, 2014). Research *in vitro* showed that ATP acts in synergy with Hsp60 to activate HBV pol (Fig. 1) (Park and Jung, 2001). It suggests that the bond between Hsp60 and HBV pol is transient and activation of the enzyme follows its dissociation from the Hsp60-HBV pol complex. Moreover, studies *in vivo* provided evidence that Hsp60 does not undergo encapsidation within the viral nucleocapsid. These findings indicate that the enzyme liberation from Hsp60-HBV pol complex precedes encapsidation. Research *in vitro* showed that at least one of two HBV pol fragments of amino acid residues 1–199 of terminal protein (TP) domain and 680–842 of Rnase H (RH) are necessary for Hsp60 binding (Park *et al.*, 2002).

Apart from the action at the cellular level, Hsp60 also has a systemic influence on the host immune response to HBV (Fig. 1). Viral infection leads to increase in Hsp60 release from infected cells to extracellular environment. Research showed that the level of serum sHsp60 is significantly higher in patients suffering from chronic hepatitis B than in patients with hepatitis C or in healthy individuals. Increased level of sHsp60 seems to be an effect of the stress caused by viral replication, because Hsp60 level in the serum showed clear correlation to the amount of HBV DNA. Significant change in the amount of sHsp60 has immunological implications since extracellular Hsp60 influences the host immune response (Kondo *et al*., 2010). Research showed that sHsp60 has a significant impact on B cell activity and activation of B lymphocyte proliferation. Moreover, it enhances IL-10 secretion from those cells *via* TLR4 signaling pathway (Cohen-Sfady *et al.*, 2005). IL-10 was previously called a cytokine synthesis inhibitory factor (CSIF) (Porrini *et al*., 1995) due to its anti-inflammatory properties. It influences mechanisms involved, both, in the first and in the second line of immune defense (Kalampokis *et al*., 2013). IL-10 decreases the synthesis of pro-inflammatory cytokines and alters the expression of major histocompatibility complex (MHC) class II proteins (Alsahafi *et al*., 2015) leading to down-regulation of T lymphocyte activity (Kalampokis *et al*., 2013). *In vitro* studies showed that elevation of production and release of IL-10 by B cell subsets results in a decrease in synthesis of monocyte cytokines (Iwata *et al*., 2011). Moreover, B cells exert a suppressive effect on antigen (Ag) presentation by DCs (Matsushita *et al*., 2010). In summary, sHsp60 enhances IL-10 production by B cells which account for the immunosuppressive effects in humans during infection of HBV corresponding with clinical studies indicating that HBV exerts active immunosuppressive effects in infected patients (Busca and Kumar, 2014).

In addition to sHsp60 release, chronic HBV infection also interferes with the host immune response mechanisms by influencing population of $CD4^+CD25^+$ T regulatory (Treg) lymphocytes (Xu *et al*., 2006). In normal conditions, Tregs produce IL-10 to maintain immunotolerance and regulate the immune system during inflammation (Busca and Kumar, 2014). HBV infection leads to an increase in Tregs population in peripheral blood and liver of severe chronic hepatitis B patients. The frequency of circulating Tregs is correlated with the HBV load in serum. These findings suggest that Tregs activity influences the viral replication level as well as Tregs are important for HBV persistence (Xu *et al*., 2006). Meanwhile, during HCV infection, Tregs are partially responsible for immune dysregulation and thus for inhibition of host immune response to viral infection (Peng *et al*., 2008; Stoop *et al*., 2005). Research *in vitro* showed that circulating Tregs inhibit HBV-specific T-cell responses by suppressing the proliferation and IFN-γ secretion by peripheral blood mononuclear cells (PBMCs) under stimulation with HBV surface antigen (HbsAg). Tregs possibly inhibit activity of PBMCs *via* direct cell-cell contact, because administration of monoclonal antibodies against programmed death-1 (PD-1) and cytotoxic lymphocyte antigen-4 (CTLA-4) slightly increases cell proliferation and significantly increases production of IFN-γ by PBMCs cocultured with Tregs. It is speculated that in *in vivo* conditions IL-10 may contribute synergistically with a cell-contact mechanism to suppressive effect (Peng *et al*., 2008; Stoop *et al*., 2005). HBV utilizes HBV core antigen (HbcAg) to stimulate Tregs to produce and secrete immune suppressive factors, such as IL-10 and transforming growth factor β (TGF-β) (Barboza *et al.*, 2007). Research *in vitro* indicates that Hsp60 may increase Tregs sensitivity to HbcAg peptide presented in the context of MHC class II molecules. Hsp60 affects Tregs *via* TLR2 signaling, elevates population of HbcAg-specific $CD4^+CD25^+$ cells and increases their IL-10 secretion activity (Kondo *et al*., 2010).

3. Hsp60 in HIV infection

HIV belongs to the *Retroviridae* family and represents the *Lentivirus* genus. It is the etiological agent of acquired immune deficiency syndrome (AIDS) (Minardi da Cruz *et al*., 2013). HIV has a diploid genome containing two positive-strand RNA copies. One of the viral enzymes – reverse transcriptase (RT) is essential for replication of HIV and other lentiviruses. This process requires viral genomic RNA to undergo retrotranscription into DNA intermediate product. After its integration into the host cell genome, DNA intermediate serves as a template for the host RNA polymerase II to synthesize viral RNA that may act as mRNA encoding HIV proteins. On the other hand, newly synthesized viral RNA may undergo encapsidation into viral nucleocapsids (Chamond *et al*., 2010; Smith and Daniel, 2006).

Hsp60 influences the course of HIV infection by interacting with one of the viral proteins – gp41. Research showed that gp41 P18 fragment, including extracellular domain (aa 539–684) is involved in Hsp60 binding. Gp41 is an envelope transmembrane protein that anchors HIV surface protein gp120 to the viral envelope. As the protein responsible for the fusion of the viral envelope with the host cell membrane, gp41 is involved in the process of viral entry into the cell (Speth *et al.*, 1999). Three transmembrane subunits of gp41 make a functional complex with three exterior subunits of gp120 and form envelope glycoprotein (Env) trimer. Binding of gp120 to host cell receptors, such as CD4 and CCR5/CXCR4, induces Env conformational changes that are followed by the gp41-mediated fusion between HIV envelope and host cell membrane (Alsahafi *et al*., 2015). Viral gp41

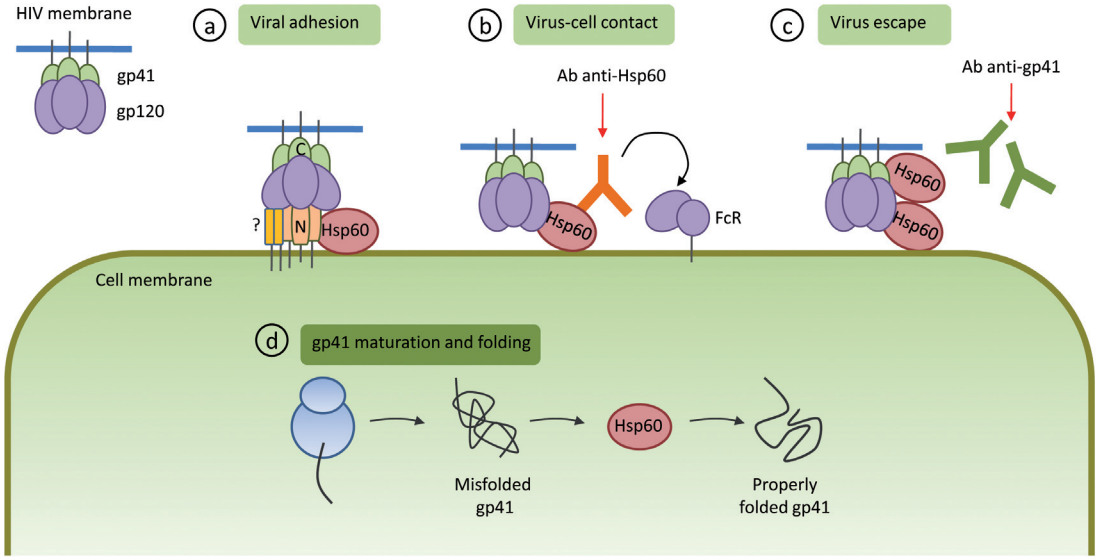

Fig. 2

The possibilities of the biological relevance of Hsp60-gp41 interaction during HIV infection

(a) Hsp60 expressed at the cell surface may bind gp41 and enable its interaction with a transmembrane receptor. **(b)** Hsp60 may help to anchor the viron to the cell surface directly through ability of Hsp60 to bind cellular proteins or indirectly through induction of auto-antibodies that bind Hsp60 and facilitate interaction between the virus and the host cell *via* Fc receptors. **(c)** Hsp60 may modulate gp41 antigenicity and help the virus to escape from antiviral immune responses. **(d)** Hsp60 may chaperone gp41 and enable a newly synthesized protein to achieve its proper conformation.

also plays an immunosuppressive role by affecting immune cells (Speth *et al.*, 1999). HIV infection leads to decrease in the number of $CD4^+$ T cells. There are many hypotheses about the mechanisms of $CD4^+$ T cell depletion; however increasing evidence indicates that gp41 is responsible for the loss of these lymphocytes. Gp41 plays a key role in regulation of the expression of NKp44L that is an activator ligand for NKp44, the natural cytotoxicity receptor of NK cells. Research shows that specific gp41 motif called 3S is essential for NKp44L translocation to the plasma membrane and thus for intensification of autologous NK cell lysis (Fausther-Bovendo *et al.*, 2010).

Gp41 may also undergo enzymatic cleavage by matriptase, a protease localized at the surface of host epithelia. As a result of this process, the peptide fragment of gp41 ectodomain is released to the extracellular environment where it performs its chemotactic activity. It affects monocytes/macrophages and neutrophils *via* their formyl peptide receptor 2 (FPR2) (Wood *et al.*, 2014). Monocyte/macrophages fulfill important role in HIV infection spread in the host organism. They are resistant to cytopathic effect and able to survive viral infection to serve as HIV reservoir for a long time (Kędzierska and Crowe, 2002; Kumar *et al.*, 2014; Kumar and Herbein, 2014). Therefore the peptide product of gp41 enzymatic cleavage seems to contribute with its chemotactic activity to virus dissemination in the body (Wood *et al.*, 2014).

There are at least 4 hypotheses to explain the importance of Hsp60-gp41 interaction in HIV infection (Fig. 2). According to the first one, Hsp60 expressed at the cell surface facilitates viral adhesion to the host cell, and thus elevates HIV infectivity. It favors the anchoring of the virion to the cell, and therefore promotes contact between gp120 and its specific cell surface receptors. The second hypothesis suggests that Hsp60 favors virion-host cell contact through induction of anti-Hsp60 auto-antibodies binding. Auto-antibody binding to Hsp60 mediates interaction between HIV and the host cell through Fc receptors. The third hypothesis indicates the possible role of Hsp60 in HIV escape from the immune system through modulation of gp41 antigenicity. Hsp60 may bind to gp41 to make it unrecognizable by anti-gp41 antibodies. According to the fourth hypothesis, Hsp60 may bind chaperone gp41 and other HIV envelope proteins. Non-mitochondrial Hsp60, involved in processes, such as protein folding and maturation, allows newly synthesized gp41 to acquire functional conformation (Speth *et al.*, 1999).

4. Hsp60 in influenza A virus infection

Influenza A virus belongs to the *Orthomyxoviridae* family (Iwasaki and Pillai, 2014) and is the etiological agent of influenza. Moreover, influenza B and C viruses may cause

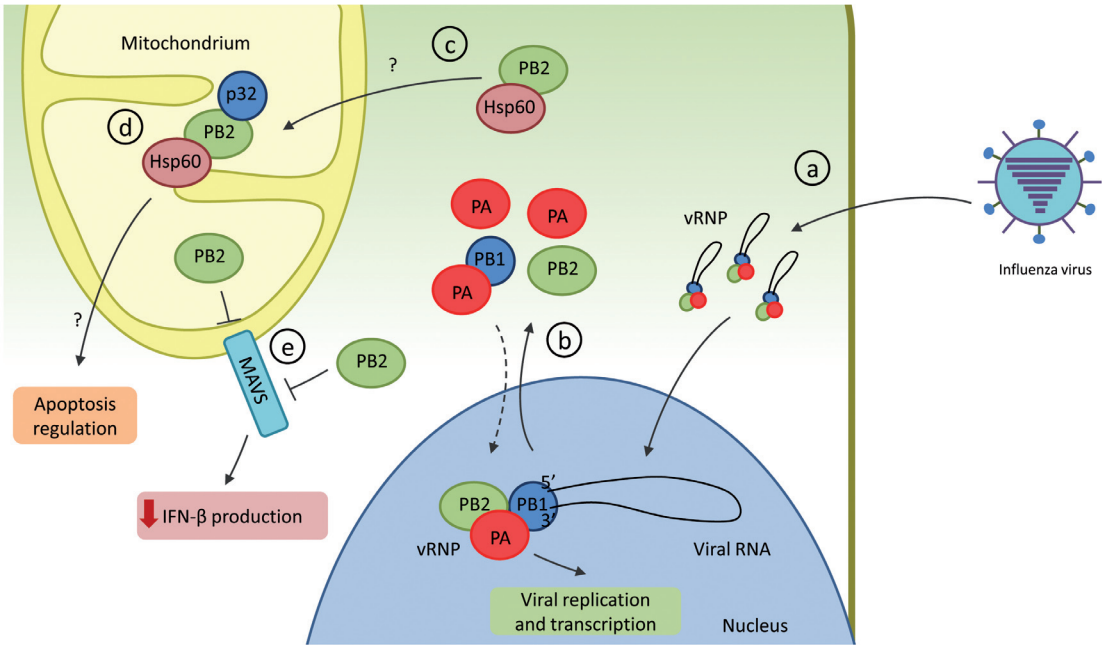

Fig. 3

The role of Hsp60 during influenza virus infection

(a) Influenza virus is endocytosed and then, after the fusion of viral and endosomal membranes, the viral ribonucleoproteins (vRNPs) are released into the cytoplasm and transported into the nucleus. vRNPs are composed of the genomic RNA segments, the three subunits of the viral RNA-dependent RNA polymerase [PB1 (polymerase basic protein 1), PB2 (polymerase basic protein 2) and PA (polymerase acidic protein)] and the nucleoprotein (NP). Within the nucleus vRNPs participate in the synthesis of viral mRNAs, which are exported to the cytoplasm **(b)** and translated into proteins by cellular ribosomes. Newly synthesized PB1, PB2, and PA proteins are transported into the nucleus: PB1 and PA are transported as a dimeric complex, whereas PB2 subunit is transported separately. **(c)** PB2 protein may associate with the cytosolic Hsp60 suggesting that Hsp60 might be involved in the transport of the PB2 protein into the mitochondria. **(d)** In mitochondria PB2 subunit may associate with protein p32 and Hsp60 and such interaction determines the anti-apoptotic effect of PB2. (**e**) PB2 protein may also interact with the mitochondrial antiviral signaling protein (MAVS) and inhibit MAVS-mediated interferon (IFN)-β production.

this disease as well (Suzuki and Nei, 2002). The genome of influenza A virus is composed of 6–8 segments, each with a single-stranded RNA of negative polarity that forms ribonucleoprotein complexes (vRNPs). Viral RNA (vRNA) replication takes place in the host nucleus and requires viral enzyme – RNA-dependent RNA polymerase. Replication is a two-step process. The first step involves the synthesis of positive-sense complementary RNA (cRNA) and the second one requires the production of negative-sense progeny vRNA at the template of cRNA intermediate (Newcomb *et al.*, 2009; Resa-Infante *et al.*, 2011). Viral nucleocapsid is enclosed by the cell-derived envelope membrane containing hemagglutinin (HA) and neuraminidase (NA) on its surface (Gao *et al.*, 2012). HA and NA are glycoproteins that determine the subtype of the virus (Iwasaki and Pillai, 2014). In the mature virion, HA and NA are stabilized by the matrix protein 1 (M1) by the formation of a matrix layer underneath the lipid bilayer of the viral envelope. Moreover, M1 directly interacts with vRNP and mediates its import to the nucleus for the synthesis of vRNA (Safo *et al.*, 2014). Besides HA and NA, the viral membrane also contains the matrix protein 2 (M2) that possesses proton channel activity. Activated M2 channel facilitates migration of vRNP into the host cell cytoplasm. Moreover, M2 participates in inflammasome activation and alters autophagosome maturation (Cho *et al.*, 2015).

Hsp60 has been found to be crucial for influenza A virus replication in a genome-wide RNA interference (RNAi) screen (Karlas *et al.*, 2010). Hsp60 interacts with polymerase basic protein 2 (PB2), which is one of the viral RNA-dependent RNA polymerase subunits (Fig. 3) (Graef *et al.*, 2010; Fodor, 2013). PB2 preferentially occurs in the host cell nucleus, but may also localize to mitochondria, where it stabilizes mitochondrial potential and plays a role in maintaining mitochondrial functionality during viral infection. Mitochondrial PB2 can affect the activity of mitochondrial antiviral signaling protein (MAVS). MAVS-PB2 interaction modulates the host immune response by leading to decrease in interferon (IFN)-β production (Fislová *et al.*, 2010). PB2 occurs in association with mtHsp60. It suggests that Hsp60 is responsible for transport of PB2 from cytosol to mitochon-

drial matrix. Therefore, the activity of Hsp60 determines the effect of PB2 on both mitochondrial stability and the level of IFN-β production (Fislová *et al.*, 2010; Graef *et al.*, 2010).

5. Conclusions

Hsp60 plays an important role in certain viral infections of the humans. This chaperone protein is able to promote infections caused by HBV, HIV and influenza A virus. Viral colonization of the host may require cytoplasmic, mitochondrial, surface and/or soluble form of Hsp60. This chaperone may interact with some proteins that are involved in viral replication cycle at different stages, such as virus attachment to the host cell or replication of the viral genetic material. Hsp60 may also be involved in regulation of the host cell apoptosis in order to synchronize cell viability and the viral replication cycle. Moreover, Hsp60 is able to influence the host immune response to viral infection. This protein may play a role in regulation of production and secretion of cytokines as well as it may affect the amount of immune cells and their function. Because interactions between Hsp60 and viral proteins are crucial for viral life cycle, chaperones should be studied extensively in order to find a new target for effective antiviral therapy.

Acknowledgments. The authors would like to thank Dr. Felix N. Toka for review of the manuscript. This work was supported by the grant No. UMO-2011/03/B/NZ6/03856 from the National Science Center in Cracow, Poland.

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