Roles of HSP on Antigen Presentation

Kazuyuki Furuta and Taka Eguchi

Abstract

Introduction Antigen presentation to T cells by dendritic cells is an essential response for the initiation of acquired immunity to eliminate pathogens that have invaded. The pathogen-derived antigens incorporated by dendritic cells are processed into peptides and presented by MHC molecules. There are also mechanisms by which cytoplasmic antigens are presented by MHC molecules. However, it has not been recognized how the HSP family involves antigen presentation. In here, we summarize the current knowledge about the roles of HSP family proteins in antigen presentation.

Methods We review; (i) mechanisms of antigen presentation by dendritic cells, (ii) roles of HSP in antigen presentation by MHC-I, and (iii) roles of HSP in antigen presentation by MHC-II.

Results Recently, the involvement of the HSP family has been revealed at several steps in the process of antigen presentation. In particular, the functions of HSP90 in the MHC-I pathway and the functions of HSP70 in the MHC-II pathway are being elucidated. However, several unsolved questions have still remained. For example, does the same mechanism function in all antigen-presenting cells? Is there specificity for antigen proteins in the HSPs? In addition, the involvement of the other HSPs in antigen presentation is still unclear.

K. Furuta (✉)
Division of Pharmaceutical Sciences, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan
e-mail: furutak@okayama-u.ac.jp

T. Eguchi (✉)
Department of Dental Pharmacology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan
e-mail: eguchi@okayama-u.ac.jp; eguchi.takanori@gmail.com

Heat Shock Proteins (2021) 21: 275–280
https://doi.org/10.1007/7515_2020_5

Published Online: 22 July 2020

Conclusions Since acquired immunity is important for the elimination of pathogens and tumors, antigen presentation should be a promising target for immunotherapy for infectious diseases and cancers. HSPs may be a potential target for manipulation of antigen presentation.

Keywords Antigen presentation · Autophagy · Dendritic cells · HSP · MHC-I · MHC-II

Abbreviations

CMA	chaperon-mediated autophagy
CTL	cytotoxic T lymphocyte
DC	dendritic cell
ER	endoplasmic reticulum
MHC	major histocompatibility complex
MIIC	MHC-II compartment
TAP	Transporter associated with antigen processing

1 Introduction

Mammals possess two types of immune responses, that is, innate immunity and acquired immunity. Innate immunity is activated against broad rages of pathogens nonspecifically by recognizing pathogen patterns. On the other hand, acquired immunity responds specifically to invaded pathogens. To recognize pathogens in the acquired immune response, dendritic cells (DCs) take pathogens by phagocytosis, and pathogen-derived proteins are fragmented to peptides by intracellular proteases. As a result, the antigen peptides bind to major histocompatibility complex class I or class II molecules (MHC-I or MHC-II) inside the cells, and the antigen-bound MHCs are presented on the cell surface. Moreover, DCs also have a mechanism to present cytoplasmic antigens by MHCs. Many researches have been conducted to elucidate the transport pathways of the antigens to both MHC-I and MHC-II. Recently, the involvement of HSP family proteins in these pathways has also been found.

1.1 Mechanisms of Antigen Presentation by Dendritic Cells

In the acquired immune response, pathogen-derived antigen peptides are presented from DCs to T cells using cell surface MHC molecules (MHC-I or MHC-II). MHC-I presents antigens to $CD8^+$ T cells, also called cytotoxic T lymphocytes (CTLs), whereas MHC-II presents antigens to $CD4^+$ T cells, also called helper T cells.

Classically, MHC-I was thought to bind and present intracellular cytoplasmic antigens such as an infected virus-derived peptide. Cytoplasmic antigens are processed to peptides by proteasomes, and the generated peptides enter the ER through a peptide transporter, TAP, where the peptides bind to MHC-I [3]. DCs also present antigens that are taken up from outside the cells by MHC-I. This mechanism is called cross-presentation and is necessary for the activation of CTLs to kill virus-infected cells and tumor cells [3, 11]. There are two pathways for the antigen cross-presentation by MHC-I. One is a cytoplasmic pathway, which is TAP-dependent, and antigens are once transferred in the cytosol and internalized in the ER through TAP. The other is the vacuolar pathway, which is TAP independent. The antigens bind directly to MHC-I within the phagosomes or the endosomes. ([2, 11]; Fig. 1).

MHC-II binds and presents exogenous antigens such as extracellular bacterium-derived proteins. The antigens are taken into cells by uptake mechanisms such as phagocytosis or endocytosis and then transported to the intracellular vesicle, MHC-II compartment (MIIC), where MHC-II is localized [17]. Furthermore,

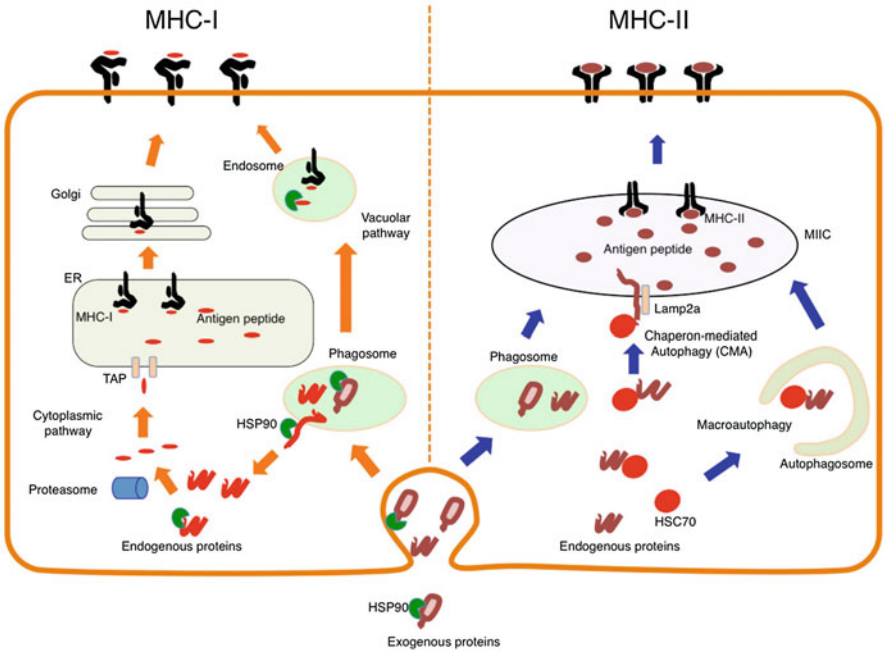

Fig. 1 Role of HSP in antigen presentation. Dendritic cells present antigen through the MHC-I or MHC-II pathway. HSP assists in the antigen presentation in various ways. In the MHC-I pathway, extracellular HSP90 assists in the uptake of exogenous antigens into the cells. In the cytoplasm, HSP90 assists in the transfer of antigen from the phagosome to the cytoplasm. In the MHC-II pathway, HSP70 binds to the antigen in the cytoplasm and assists in the translocation of MHC-II to MIIC by chaperone-mediated autophagy. HSC70 also assists in the transfer of cytoplasmic antigens into autophagosomes for macroautophagy

MHC-II also presents intracellular antigens through another mechanism by which cytoplasmic antigens enter MIIC by autophagy. This mechanism is thought to be important for the presentation of cytoplasmic pathogens-derived antigens [18]. This mechanism of cytoplasmic antigen presentation is also required for the presentation of self-antigens to $CD4^+$ T cells to induce immune tolerance [6, 15].

1.2 Roles of HSP in Antigen Presentation by MHC-I

HSP has been reported to regulate antigen presentation by binding to antigen proteins as a molecular chaperone protein. The role of HSP in MHC-I-mediated antigen presentation has been well studied. Extracellular HSP90 binds to exogenous antigens outside the cell and assists in the uptake of the antigen to the cross-presentation pathway. It has been observed that extracellular HSP90-ovalbumin (OVA) protein complexes are transported to the early endosome and enter the cross-presentation pathway [19]. Since the internalized HSP90-OVA complex is colocalized with proteasomes in the cytosol, HSP90 could be involved in the TAP-dependent cross-presentation pathway and play a key role in promoting the transition of the antigen from the endosomes to the cytosol [16]. HSP90 has been reported to assist in the cross-presentation of tumor-derived antigens. However, in this case, the cross-presentation pathway has shown to be a TAP-independent vacuolar pathway [14]. The cytoplasmic HSP90 is also involved in cross-presentation. HSP90α was shown to be required for the cytoplasmic transition of antigens by using HSP90 inhibitors. In addition, cross-presentation was reduced in HSP90α-deficient DCs, although the presentation of cytosolic antigens by MHC-I was not affected [7, 9, 10, 20]. HSP other than HSP90 is also involved in cross-presentation. Hsp70 and gp96 (also known as Grp94 or Hsp90B) were reported to assist in the uptaking of exogenous antigens [1].

1.3 Roles of HSP in Antigen Presentation by MHC-II

The role of HSP in antigen presentation by MHC-II is not as well understood as MHC-I. HSP90 has been reported not to promote MHC-II-mediated antigen presentation of exogenous antigens derived from OVA protein [16]. On the other hand, it has also been reported that MHC-II-mediated presentation of extracellular glutamate decarboxylase (GAD)-derived peptides was promoted by HSP90 [8]. Therefore, the role of extracellular HSP90 on MHC-II-mediated antigen presentation may depend on the antigen proteins.

The role of cytoplasmic HSP in MHC-II-mediated antigen presentation has also been reported. One of the roles of cytoplasmic HSC70 is chaperone-mediated autophagy (CMA). In CMA, proteins are transported into the autophagosomes by a lysosomal transmembrane protein Lamp2a [12]. HSC70 assists in the association

of the antigens to Lamp2a during CMA [21]. Several endogenous antigens are reported to be transferred into the autophagosome by CMA and presented by MHC-II [4, 21]. HSP70 has also been reported to involve in macroautophagy-mediated antigen presentation by MHC-II. HSC70 assists in the transition of proteins into autophagosomes [5, 13].

2 Conclusions

Many studies have revealed the roles of HSPs in antigen presentation. In particular, the functions of HSP90 in the MHC-I pathway and the functions of HSP70 in the MHC-II pathway are being elucidated. However, several unsolved questions have still remained. For example, does the same mechanism function in all antigen-presenting cells? Is there specificity for antigen proteins in the HSPs? In addition, the involvement of the other HSPs in antigen presentation is still unclear. Since acquired immunity is important for the elimination of pathogens and tumors, antigen presentation should be a promising target for immunotherapy for infectious diseases and cancers. HSPs may be a potential target for manipulation of antigen presentation.

Acknowledgements We thank Dr. Stuart K. Calderwood, Dr. Kuniaki Okamoto, Dr. Paul Roche and Dr. Satoshi Tanaka for useful discussion and continuous support. This work was supported in part by JSPS KAKENHI, grant numbers 17K08273 (KF), 17K11642 (TE), SUZUKEN memorial foundation (KF, TE), Smoking Research Foundation (KF), and Koyanagi Foundation (KF).

Disclosure of Interests All authors declare they have no conflict of interest.

Ethical Approval for Studies Involving Humans This article does not contain any studies with human participants performed by any of the authors.

Ethical Approval for Studies Involving Animals This article does not contain any studies with animals performed by any of the authors.

References

1. Binder RJ, Blachere NE, Srivastava PK (2001) Heat shock protein-chaperoned peptides but not free peptides introduced into the cytosol are presented efficiently by major histocompatibility complex I molecules. J Biol Chem 276:17163–17171
2. Blander JM (2018) Regulation of the cell biology of antigen cross-presentation. Annu Rev Immunol 36:717–753
3. Cresswell P, Ackerman AL, Giodini A, Peaper DR, Wearsch PA (2005) Mechanisms of MHC class I-restricted antigen processing and cross-presentation. Immunol Rev 207:145–157
4. Deffit SN, Blum JS (2015a) A central role for HSC70 in regulating antigen trafficking and MHC class II presentation. Mol Immunol 68:85–88

5. Deffit SN, Blum JS (2015b) Macronutrient deprivation modulates antigen trafficking and immune recognition through HSC70 accessibility. J Immunol 194:1446–1453
6. Duraes FV, Niven J, Dubrot J, Hugues S, Gannage M (2015) Macroautophagy in endogenous processing of self- and pathogen-derived antigens for MHC class II presentation. Front Immunol 6:459
7. Graner MW (2016) HSP90 and immune modulation in cancer. Adv Cancer Res 129:191–224
8. Houlihan JL, Metzler JJ, Blum JS (2009) HSP90alpha and HSP90beta isoforms selectively modulate MHC class II antigen presentation in B cells. J Immunol 182:7451–7458
9. Ichiyanagi T, Imai T, Kajiwara C, Mizukami S, Nakai A, Nakayama T, Udono H (2010) Essential role of endogenous heat shock protein 90 of dendritic cells in antigen cross-presentation. J Immunol 185:2693–2700
10. Imai T, Kato Y, Kajiwara C, Mizukami S, Ishige I, Ichiyanagi T, Hikida M, Wang JY, Udono H (2011) Heat shock protein 90 (HSP90) contributes to cytosolic translocation of extracellular antigen for cross-presentation by dendritic cells. Proc Natl Acad Sci U S A 108:16363–16368
11. Joffre OP, Segura E, Savina A, Amigorena S (2012) Cross-presentation by dendritic cells. Nat Rev Immunol 12:557–569
12. Kaushik S, Cuervo AM (2018) The coming of age of chaperone-mediated autophagy. Nat Rev Mol Cell Biol 19:365–381
13. Kettern N, Rogon C, Limmer A, Schild H, Hohfeld J (2011) The Hsc/Hsp70 co-chaperone network controls antigen aggregation and presentation during maturation of professional antigen presenting cells. PLoS One 6:e16398
14. Kurotaki T, Tamura Y, Ueda G, Oura J, Kutomi G, Hirohashi Y, Sahara H, Torigoe T, Hiratsuka H, Sunakawa H et al (2007) Efficient cross-presentation by heat shock protein 90-peptide complex-loaded dendritic cells via an endosomal pathway. J Immunol 179:1803–1813
15. Munz C (2016) Autophagy beyond intracellular MHC class II antigen presentation. Trends Immunol 37:755–763
16. Oura J, Tamura Y, Kamiguchi K, Kutomi G, Sahara H, Torigoe T, Himi T, Sato N (2011) Extracellular heat shock protein 90 plays a role in translocating chaperoned antigen from endosome to proteasome for generating antigenic peptide to be cross-presented by dendritic cells. Int Immunol 23:223–237
17. Roche PA, Furuta K (2015) The ins and outs of MHC class II-mediated antigen processing and presentation. Nat Rev Immunol 15:203–216
18. Schmid D, Pypaert M, Munz C (2007) Antigen-loading compartments for major histocompatibility complex class II molecules continuously receive input from autophagosomes. Immunity 26:79–92
19. Tanaka T, Okuya K, Kutomi G, Takaya A, Kajiwara T, Kanaseki T, Tsukahara T, Hirohashi Y, Torigoe T, Hirata K et al (2015) Heat shock protein 90 targets a chaperoned peptide to the static early endosome for efficient cross-presentation by human dendritic cells. Cancer Sci 106:18–24
20. Udono H (2012) Heat shock protein magic in antigen trafficking within dendritic cells: implications in antigen cross-presentation in immunity. Acta Med Okayama 66:1–6
21. Zhou D, Li P, Lin Y, Lott JM, Hislop AD, Canaday DH, Brutkiewicz RR, Blum JS (2005) Lamp-2a facilitates MHC class II presentation of cytoplasmic antigens. Immunity 22:571–581