ER stress proteins in autoimmune and inflammatory diseases

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Over the past two decades, heat shock proteins (HSPs) have been implicated in inflammatory responses and autoimmunity. HSPs were originally believed to maintain protein quality control in the cytosol. However, they also exist extracellularly and appear to act as inflammatory factors. Recently, a growing body of evidence suggested that the other class of stress proteins such as, endoplasmic reticulum (ER) stress proteins, which originally act as protein quality control factors in the secretory pathway and are induced by ER stress in inflammatory lesions, also participate in inflammation and autoimmunity. The immunoglobulin heavy-chain binding protein (Bip)/glucose-regulated protein 78 (GRP78), calnexin, calreticulin, glucose-regulated protein 94 (GRP94)/gp96, oxygen regulated protein 150 (ORP150)/glucose-regulated protein 170 (GRP170), homocysteine-induced ER protein (Herp) and heat shock protein 47 (hsp47)/Serpin H1, which are expressed not only in the ER but also occasionally at the cell surface play pathophysiological roles in autoimmune and inflammatory diseases as pro- or anti-inflammatory factors. Here we describe the accumulating evidence of the participation of ER stress proteins in autoimmunity and inflammation and discuss the critical differences between the two classes of stress proteins.

Keywords: autoimmunity, inflammation, ER stress, ERAD, molecular chaperone

INTRODUCTION

Inflammation is a typical sign of autoimmune diseases. Misdirected immune responses target self-antigens and induce severe inflammatory responses, which sometimes cause death. In addition to numerous components in autoimmune responses, heat shock proteins (HSPs) have been implicated in autoimmune and inflammatory diseases over the past two decades (Hauet-Broere et al., 2006; Van Eden et al., 2007). Many HSPs are so-called molecular chaperones and folding enzymes, which maintain protein folding in a cell (Bukau et al., 2006; Hartl, 2011). Because protein folding is easily impaired by various cytotoxic stresses, such as heat shock, cytotoxic chemicals, hypoxia, and inflammation, prokaryotic to higher eukaryotic organisms have evolved stress responses and HSPs. The transcription of HSPs and their subsequent protein expression are stimulated by cytotoxic stresses, and they immediately restore protein folding and cellular homeostasis to counter toxic stresses (Morimoto, 1998). Thus, HSPs could be postulated to act as intracellular protein homeostasis maintenance factors. However, HSPs have also been reported to be observed in the extracellular fluid (Njemini et al., 2011), and act as pro- and anti-inflammatory factors especially in autoimmune and inflammatory diseases in diverse manners. In inflammatory lesions, HSPs are upregulated by inflammatory stress and are released into the extracellular fluid. Then, the extracellular HSPs specifically induce proinflammatory cytokines and enhance the antigenicity of autoantigens through modulations of antigen presentation (Multhoff, 2006; Yokota and Fujii, 2010). However, the extracellular HSPs can also stimulate anti-inflammatory regulatory T cell responses, thereby inducing the negative feedback control of inflammation (Hauet-Broere et al., 2006; Van Eden et al., 2007). Indeed, immunization with HSP peptides prevents disease development in autoimmune model animals, such as adjuvant arthritis and collagen-induced arthritis (CIA; van Eden et al., 1988; Jorgensen et al., 1998; Wendling et al., 2000). Presently, besides HSPs, another class of stress proteins is also known to exist in eukaryotic cells. Endoplasmic reticulum (ER) stress proteins, the specialized factors involved in protein quality control in the secretory pathway (Hoseki et al., 2010; Araki and Nagata, 2011; Smith et al., 2011), are induced by ER stress, which is very different from cytosolic stress (Mori, 2000; Walter and Ron, 2011). However, similar to HSPs, ER stress proteins are also induced by inflammatory stress (Yoshida, 2007), suggesting that ER stress proteins might also participate in autoimmune and inflammatory responses. Here, we discuss the accumulating evidence that ER stress proteins and their autoantibodies play roles in autoimmune and inflammatory diseases.

REGULAR FUNCTIONS OF ER STRESS PROTEINS

Before discussing the relevance of ER stress proteins in autoimmune diseases, we have briefly sketched the regular functions of ER stress proteins in a cell. Although the boundary between the two is ambiguous, ER stress proteins can be classified into two groups. The first group consists of molecular chaperones and folding enzymes, which assist the folding and assembly of newly synthesized proteins and prevent misfolding and aggregation of preexisting proteins. The other group consists of protein degradation factors, which mediate the clearance of proteins that should be degraded, such as misfolded proteins. The latter protein clearance
pathway is called the ER-associated degradation (ERAD) pathway (McCracken and Brodsky, 1996; Brodsky and McCracken, 1997).

The ER is located at the starting point of the protein secretory pathway. Secretory or membrane proteins are first cotranslationally transported into the ER from cytosolic ribosomes, modified and properly folded, and then translocated to the next step of the secretory pathway (Figures 1A,B; Ni and Lee, 2007; Araki and Nagata, 2011). After the ER, proteins pass through the Golgi apparatus and are finally secreted to the cell surface through a secretory vesicle. In the ER, most proteins are glycosylated and covalently crosslinked with disulfide bonds. Such protein modifications are believed necessary for the structural stabilization of the proteins destined to be secreted into the extracellular environment (Ni and Lee, 2007; Araki and Nagata, 2011). Calnexin and calreticulin are lectin-like chaperones that specifically maintain the folding of glycosylated proteins (Williams, 2006). Protein disulfide isomerase (PDI) is an oxidoreductase that mediates protein disulfide bond formation and isomerization (Tu and Weissman, 2004; Ellgaard and Ruddock, 2005). The immunoglobulin heavy-chain binding protein (Bip)/glucose-regulated protein 78 (GRP78) is a hsp70-type molecular chaperone that maintains protein folding (Ni and Lee, 2007; Araki and Nagata, 2011). Glucose-regulated protein 94 (GRP94)/gp96 and oxygen regulated protein 150 (ORP150) are hsp90 and hsp70 family molecular chaperones, respectively; their functions remain unclear (Ni and Lee, 2007; Araki and Nagata, 2011). Another characteristic stress protein in the ER is heat shock protein 47 (hsp47)/Serpin H1, the only heat shock regulated protein in the ER, is the collagen-specific molecular chaperone (Nagata, 2003; Ishida and Nagata, 2011). Using these molecular chaperones and folding enzymes, secretory and membrane proteins are properly folded in the ER and then transported to the Golgi apparatus. Other chaperones and enzymes were precisely described in a recent article (Araki and Nagata, 2011).

Improperly folded proteins are strictly retained in the ER via anchoring by ER chaperones and enter the ERAD pathway (Araki and Nagata, 2011; Smith et al., 2011). ERAD is a multi-step mechanism, which can be divided into the following three steps: (1) the substrate is recognized and isolated, (2) the substrate is dislocated from the ER into the cytosol, and (3) the substrate is then degraded by the ubiquitin proteasome system in the cytosol (Figures 1C–E; Hershko and Ciechanover, 1998). Thereby, the clearance of the proteins from the ER is completed. Among these steps, the first step is mediated by ERAD-enhancing mannosidase-like protein 1 (EDEM-1), ERdj5, Bip, Osteosarcoma 9 (OS9), XTP3 transactivating gene B (XTP3B), and SEL1L (Hosokawa et al., 2001; Ushioda et al., 2008; Hagiwara et al., 2011; Ushioda and Nagata, 2011). The substrate is directly transferred from the calnexin/calreticulin-mediated folding cycle to the EDEM-1-containing degradation recognition complex (Molinari et al., 2003; Oda et al., 2003). The substrate is then transferred from EDEM-1 and SEL1L to the so-called ERAD complex, postulated to form a protein dislocation channel (Mueller et al., 2006, 2008; Christianson et al., 2008).
ER STRESS

The stress response for HSPs, called heat shock response, is mediated by transcription factors called heat shock factors (HSFs; Morimoto, 1998). Similarly, the stress response for ER stress proteins, called the unfolded protein response (UPR), is mediated by the unconventional transcription factors, ATF6 and XBP1, and a translation and apoptosis regulating factor, PERK (Figure 2; Mori, 2000; Walter and Ron, 2011). The UPR can be experimentally stimulated by chemical compounds that specifically interfere with protein glycosylation and disulfide bond formation because these protein modifications are necessary for the structural stability of secretory and membrane proteins. In addition, perturbation of calcium storage in the ER causes impairments in the quality of ER proteins because the ER has a high calcium concentration, and many of the ER proteins need calcium ions. Alternatively, the UPR is physiologically activated during plasma cell differentiation in order to expand the protein folding capacity for massive production of immunoglobulins. The activation of the UPR has been observed in various neurodegenerative diseases, inflammatory diseases, and viral infections (Yoshida, 2007). Thus, the UPR can be postulated as a completely independent pathway from cytosolic stresses. Both cytosolic and ER stresses are commonly stimulated by inflammation. Although several studies suggest that ER stress protein levels correlate with inflammatory pathogenesis, the roles of ER stress and ER stress proteins in autoimmune and inflammatory diseases remain unclear. Thus, in addition to the heat shock response, the other axis of the cellular stress response might provide new insights into disease mechanisms and clinical treatments.

FIGURE 2 | Schematic representation of two distinct stress responses. When misfolded proteins accumulate in the ER, they perturb ER protein homeostasis and organelle functions. Such perturbations are called ER stressors (A). ER stress leads to the activation of membrane spanning stress sensors. ATF6 is a membrane spanning transcription factor that is processed and released from the ER membrane under ER stress, and the stress signal is then transmitted to the nucleus. IRE1 and PERK activate the transcription factors, XBP1 and ATF4, and stimulate a stress response. Such stress responses are called an unfolded protein response (UPR) (B). UPR leads to an upregulation of ER stress proteins, which consist of molecular chaperones and folding enzymes, and ERAD recognition and dislocation factors. Such cross-membrane signal transduction is very different from the heat shock response (HSR (C)). When the cytosolic stresses perturb the cytosolic protein homeostasis, heat shock factor (HSF) is activated and transmits the signal into the nucleus. Then, an upregulation of HSPs is induced. It is a challenge to recover cytosolic protein homeostasis.
from inflammatory stress during RA progression, and they might have no pathophysiological roles. Because the UPR is stimulated through inflammation and ER stress proteins, including Bip, are subsequently induced (Yoshida, 2007), Bip could be simply a specific and abundant autoantigen in the inflammatory lesion that is unrelated to RA pathogenesis. Second, the autoantigen might act as an anti-inflammatory factor, similar to HSPs. Several studies suggested that extracellular Bip stimulates the production of the anti-inflammatory cytokines, IL-4 and IL-10, through specific T lymphocytes (Blass et al., 2001; Corrigall et al., 2001, 2004; Bodman-Smith et al., 2003; Brownlie et al., 2006; Panayi and Corrigall, 2006). Furthermore, the pre-administration of Bip protein to mice prevents the in vivo induction of adjuvant arthritis or CIA, both of which are well-known artificial models of autoimmune diseases (Corrigall et al., 2001; Brownlie et al., 2006). Third, the Bip antigen could act as a proinflammatory factor. Bip positively causes immunological responses and inflammation. Recently, Shoda et al. (2011) reported that in addition to the intact Bip antibody, anticitrullinated Bip (ctBip) antibody is frequently detected in RA patients. The ctBip protein, but not intact Bip, enhances anticitrullin antibodies and worsens arthritis symptoms in a mouse model of adjuvant arthritis. Citrullination is protein modification in which an arginine residue is converted into a citrulline residue by a specific intracellular enzyme, peptidylarginine deiminase (PAD; Vossenaar et al., 2003). The anti-citrullinated peptide/protein antibody (ACP A) is frequently detected in RA patients (Vincent et al., 2005; Suzuki et al., 2007; van Venrooij et al., 2011). Although the reasons why citrullination is frequently observed and how it participates in RA pathogenesis remains unclear, the relationship between stress proteins and this specific protein modification suggests an undescribed crosstalk between inflammatory stress and disease-specific protein modifications in RA pathogenesis. In addition to RA, the anti-Bip autoantibody is also detected in another autoimmune and inflammatory disease, systemic lupus erythematosus (SLE; Casciola-Rosen et al., 1994; Weber et al., 2010), in which its pathophysiological role remains unknown.

**HSP47**

Hsp47 is an ER resident molecular chaperone; it is the only HSP in the ER. Hsp47 specifically maintains collagen biosynthesis (Nagata, 2003; Ishida and Nagata, 2011). Its gene disruption in mice causes significant reductions in mature collagens in connective tissues, resulting in embryonic lethality (Nagai et al., 2000; Marutani et al., 2004; Matsuoka et al., 2004). Several studies showed that the levels of anti-hsp47 autoantibody are specifically increased in RA patients (Hattori et al., 1998, 2000, 2001, 2003, 2005). However, little is known about how hsp47 and its autoantibody correlate with RA pathogenesis. In addition to RA, the levels of the autoantibody to hsp47 are also increased in other autoimmune diseases, such as SLE, Sjögren’s syndrome (SJS), mixed connective tissue disease (MCTD), systemic sclerosis (SSc), and non-specific idiopathic pneumonia (Yokota et al., 2003; Fujimoto et al., 2004; Kukugawa et al., 2008). Most of these diseases can be considered connective tissue diseases in which an upregulation of various types of collagen is observed. The expression profiles of collagens and hsp47 are fully consistent in both healthy (Masuda et al., 1998; Yamamura et al., 1998; Hirata et al., 1999; Yasuda et al., 2002) and diseased conditions (Masuda et al., 1994; Naitoh et al., 2001; Sato et al., 2008). Hsp47 might be the protein that stands at the junction of stress, the extracellular matrix (ECM) biogenesis, and autoimmune/connective tissue diseases.

**HERP**

Lupus nephritis, which is a kidney inflammatory disorder, is one of the manifestations of SLE, a complex autoimmune disease. Among the variety of autoantibodies that are detected in SLE patients, the anti-double-stranded DNA (dsDNA) antibody, which is a type of anti-nuclear antibody (ANA), is most characteristic of SLE and appears to significantly contribute to the pathogenesis of lupus nephritis (Isenberg et al., 2007). Although administration of dsDNA failed to initiate antibody production (Madaio et al., 1984), nucleosome-forming dsDNA elicited the anti-dsDNA antibody production (Rumore and Steinman, 1990; Casciola-Rosen et al., 1994; Vosnava et al., 2005), suggesting that proteins like histone can work as an adjuvant for enhancing the antigenicity of dsDNA. Another possibility for anti-dsDNA antibody production is elicitation by cross-reactive protein antigens. Several proteins have been reported to cross-react with the anti-dsDNA antibody (Isenberg et al., 2007). Among them, α-actinin, which is an actin-associated protein, might be a potent candidate for the original antigen, which evokes anti-dsDNA antibody production (Mostoslavsky et al., 2001; Decharan et al., 2002). However, a dysregulation of the negative selection of B-cell clones, which produce autoantibodies, occurs in these diseases.

Recently, Herp was suggested as a possible cross-reactive antigen of the anti-dsDNA antibody (Hirabayashi et al., 2010). Herp is an ER resident membrane protein that is involved in the ERAD complex and is induced by UPR (Kokame et al., 2000, 2001; Okuda-Shimizu and Hendershot, 2007; Kny et al., 2011; Marutani et al., 2011). Thus, Herp is an ER stress protein, can be induced by inflammatory ER stress. Among the known candidates for the original antigen of the anti-dsDNA antibody including α-actinin, only Herp can be induced by inflammatory stress. Thus, Herp can be the key component that connects inflammatory stress responses and anti-dsDNA antibody production in SLE.

**CALRETICULIN**

The anti-Ro/SS-A antibody, which is also considered an ANA, is one of the most studied and crucial markers in many autoimmune diseases, such as SLE, SjS, SSc, and RA (Anderson et al., 1962; Clark et al., 1969; Alspaugh and Tan, 1975; Schulte-Pelkm et al., 2009; Defendenti et al., 2011). Although it has a strong, well-established association with autoimmune diseases, especially with neonatal lupus, it is unclear how it participates in autoimmune diseases (Schulte-Pelkm et al., 2009; Defendenti et al., 2011). Recently, it was shown that the anti-Ro/SS-A antibody can be categorized into two types, each of which specifically recognizes the 52-kDa (Ro52) and 60-kDa (Ro60) antigens. Ro52 and Ro60 form a Ro ribonucleoprotein (RNP) complex with a couple of other proteins, while the intracellular functions and pathogenic relevancies of those antigens remain unclear (Schulte-Pelkm et al., 2009; Defendenti et al., 2011).

Calreticulin is an essential ER resident lectin-like chaperone, which is induced by ER stress (Yoshida et al., 1998; Mesea et al., 1998).
Calreticulin was first postulated as the Ro/SS-A autoantigen (Collins et al., 1989; McCauliffe et al., 1990). However, it was later demonstrated that calreticulin itself was not an antigen (Lu et al., 1993; Boehm et al., 1994), but it maintained Ro RNP complex formation through its chaperone activity and modulated the antigenicity of the complex (Cheng et al., 1996; Staikou et al., 2003). Although it was shown that calreticulin was not the autoantigen for the Ro/SS-A autoantibody, the anti-calreticulin autoantibody has been independently observed in SLE patients (Boehm et al., 1994), complete congenital heart block (CCHB; Orth et al., 1996), which is one of the manifestations of SLE, and inflammatory bowel disease (Watanabe et al., 2006).

**CALNEXIN, GRP94, AND ORP150**

Calnexin is an ER resident lectin-like chaperone (Wada et al., 1991, 1997; Hebert et al., 1995; Deprez et al., 2005), which is not induced or is only mildly induced by ER stress (Kamauchi et al., 2005). An autoantibody to calnexin is observed in SLE patients, while its biological relevance remains unknown (Weber et al., 2010).

GRP94 is an essential ER resident hsp90 family chaperone, which is induced by cytosolic and ER stress (Wanderling et al., 2007; Eletto et al., 2010). Anti-GRP94 autoantibodies have been observed in SLE patients (Boehm et al., 1994), RA (Weber et al., 2010), and myasthenia gravis (MG; Suzuki et al., 2011). In addition, cell surface expression of GRP94 itself is detected in patients with type I diabetes (Paget et al., 2003) and in GRP94 transgenic mice (Liu et al., 2003). In GRP94 transgenic mice, lupus-like autoimmune disorder and systemic inflammation are induced, suggesting that extracellular GRP94 and its autoantibody have proinflammatory effects in autoimmune diseases.

ORP150 is an essential ER resident hsp70 family chaperone that is induced by ER stress and hypoxia (Kitao et al., 2001; Ni and Lee, 2007). An autoantibody to ORP150 is detected in patients with atherosclerosis and type I diabetes (Tsukamoto et al., 1996; Nakatani et al., 2006), but it remains unclear if they have a pathophysiological role in autoimmune responses.

**REGULATION OF ER STRESS PROTEIN DISTRIBUTION**

As discussed above, the critical difference between HSPs and ER stress proteins is based on the stress pathway they are induced through. One is through a heat shock response, and the other is through the UPR. However, another striking difference exists, i.e., HSPs are originally distributed in the cytosol. In patients with inflammatory diseases, HSPs are observed in extracellular fluid; this could be due to the destruction of the plasma membrane that accompanies stress-induced apoptosis, necrosis, and phagocytosis or alternative active secretion through exosomes. On the other hand, ER stress proteins are originally located in the secretory pathway. Thus, ER stress proteins can potentially be secreted into the cell surface, after which they escape from the ER retention mechanism. Indeed, some ER stress proteins are expressed on the cell surface without any cell destruction, e.g., calnexin (Okazaki et al., 2000), calreticulin (Jeffery et al., 2011), Bip (Delpino and Castelli, 2002), GRP94 (Altmeyer et al., 1996), and hsp47 (Hebert et al., 1999). How they escape, how they are retained, and whether this leaky expression correlates with autoimmune pathogenesis remains unknown. However, this apparent difference between the two types of stress proteins might cause physiological differences, therefore, this should be examined in autoimmune and inflammatory diseases.

**CONCLUSION**

Several studies suggested that ER stress proteins are potent immunomodulating components in autoimmune and inflammatory diseases. Although their pathogenic relevances remain unclear, some of them appear to participate in disease progression. Their inducibility by inflammatory stress and their original distribution in the secretory pathway could be advantageous for participation in autoimmune and inflammatory responses. Until now, the major evidence of the involvement of ER stress proteins in autoimmune diseases appears to be autoantigens. This situation can be compared to that of HSPs two decades ago. Since then, much has been revealed about the functions of HSPs in addition to being autoantigens. Because HSPs and ER stress proteins share several properties as molecular chaperones, we may be able to expect unidentified and important roles of ER stress proteins in autoimmune response as well as HSPs. Indeed, another issue of the stress proteins in autoimmune responses is their potential immunomodulating abilities. Because chaperones can broadly associate with other proteins, including autoantigens and recruit antigen presentation pathway, they can work as endogenous adjuvants in immune responses. In this review, we focused on the roles of ER stress proteins as autoantigens. However, several other issues that are related to ER stress are also important, e.g., HLA-B27 misfolding in ankylosing spondylitis and anti-apoptotic function of HRD1/synoviolin in synovial cells in RA (Yoshida, 2007; Todd et al., 2008; Yagishita et al., 2008; Colbert et al., 2010). At the moment, the features of ER stress proteins in autoimmunity remain largely unclear. The potential relevance of ER stress proteins in many autoimmune and inflammatory diseases makes them potential clinical targets.

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Frontiers in Immunology | Inflammation March 2012 | Volume 3 | Article 48 | 8