ANTIOXIDANTS & REDOX SIGNALING
Volume 9, Number 5, 2007

DOI: 10.1089/ars.2006.1520

Forum Review

A Novel ER Stress Transducer, OASIS, Expressed in Astrocytes

ATSUSHI SAITO,[1,2] SHIN–ICHIRO HINO,[1] TOMOHIKO MURAKAMI,[1,2]
SHINICHI KONDO,[1] and KAZUNORI IMAIZUMI[1]

ABSTRACT

Secretory and transmembrane proteins are correctly folded or processed in the endoplasmic reticulum (ER). Various stresses disturb ER function and provoke the accumulation of unfolded proteins in the ER lumen. This condition is termed ER stress. Recently, ER stress has been linked to neuronal death in various neurodegenerative diseases. Among the cell populations in the nervous system, which comprises heterogeneous cell types including neuronal and glial cells, astrocytes have the unique ability of being able to tolerate and even proliferate under ischemic and hypoxic conditions that lead to ER stress. This review introduces a novel ER stress transducer, old astrocyte specifically induced substance (OASIS), that regulates the signaling of the unfolded protein response specifically in astrocytes and contributes to resistance to ER stress. In addition, current information is summarized regarding new types of ER stress transducers homologous to OASIS that are involved in cell type-specific ER stress responses. *Antioxid. Redox Signal.* 9, 563–571.

INTRODUCTION

THE ENDOPLASMIC reticulum (ER) is an organelle in which secretory and transmembrane proteins, as well as the resident proteins of the secretory pathway, are synthesized, folded, or modified. Perturbations in the efficiency of protein folding result in the accumulation of unfolded or misfolded proteins in the ER. For example, physiological or pharmacological conditions such as disturbance of calcium homeostasis, expression of mutated proteins, or ischemic insults, induce accumulation of these client proteins. These conditions, that are collectively termed ER stress, have the potential to induce cellular damage (16). Excessive or long-term stress in the ER causes apoptosis involving activation of caspases and stress kinases, including Ask1 and JNK (25, 28). The ER also contains specific signaling and effector mechanisms that sense and deal with accumulation of unfolded proteins. Major adaptive programs include the transcriptional induction of ER molecular chaperones, translational attenuation, and degradation of unfolded proteins. This defense system is conserved throughout yeast to higher eukaryotes, and termed the unfolded protein response (UPR). Research over the past several years has led to a detailed understanding of the major pathways of the UPR and death signaling induced by ER stress (reviewed in Refs. 22 and 36). Recently, there has been a prominent surge in research regarding cell type-specific responses to ER stress as the mammalian body is composed of heterogenous tissues and cells, and these varieties of cells are exposed to diverse stresses in tissue-specific manners (1, 17, 53).

Many neurodegenerative disorders have common pathological features: insoluble or malfolded proteins aggregate and are deposited in the neurons or matrix of the central nervous system (46). These proteins are inherently cytotoxic and cause neuronal damage (3). Recent studies have implicated the failure of the UPR in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (13–15, 18, 28, 44). ER stress can be also provoked by a variety of pathophysiological conditions, such as in many recessively-inherited genetic diseases that are due to loss-of-function mutations, or protein-folding mutations that interfere with cellular processes, resulting in a gain of function and a dominant pattern of inheritance. To develop therapeutic

[1]Division of Molecular and Cellular Biology, Department of Anatomy, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.
[2]Division of Structural Cellular Biology, Nara Institute of Science and Technology (NAIST), Nara, Japan.

strategies for these diseases, further insight into ER stress and its stress response is needed. In this review, we focus on a novel signaling pathway of the UPR regulated in astrocytes by a transmembrane transcription factor, OASIS (old astrocyte specifically induced substance), and also introduce the newly determined types of ER stress transducers homologous to OASIS that may function in a tissue- or cell type-specific manner.

PROXIMAL SENSORS FOR UNFOLDED PROTEINS AND SIGNALING PATHWAYS OF THE UPR

Various abnormal conditions such as the presence of unfolded or abnormally glycosylated proteins, perturbation in redox status, glucose deprivation, and disturbed intracellular Ca2+ homeostasis disrupt ER function, resulting in the accumulation of unfolded or misfolded proteins in the ER lumen; known, as already mentioned, as ER stress (40). Under ER stress, the unfolded protein response (UPR) is evoked in cells to cope with the accumulation of unfolded or misfolded proteins. In mammalian cells, PKR-like ER kinase (PERK) (9, 10), inositol-requiring and ER to nucleus signaling 1 (IRE1) (45, 47), and activating transcription factor 6 (ATF6) (11, 50) sense the presence of unfolded proteins in the ER lumen and transduce signals to the cytoplasm and the nucleus. In the cases of PERK and IRE1, which both have cytoplasmic serine/threonine kinase domains, ER stress induces lumenal-domain-driven homodimerization, autophosphorylation, and activation (2, 9, 20). In contrast, the accumulation of unfolded proteins in the ER lumen leads to ATF6 transit to the Golgi complex, where it is cleaved by the Site-1 and Site-2 proteases (S1P and S2P), generating a cytoplasmic N-terminal domain that is an active transcription factor (48).

PERK directly phosphorylates the α subunit of the eukaryotic initiation factor (eIF2α). Phosphorylation of eIF2α prevents the assembly of 80S ribosomal initiation complexes, thus inhibiting protein translation. This aspect of the UPR is shared by a number of other cellular stress responses, which activate different eIF2α kinases. Interestingly, although most cellular protein synthesis is shut down in this pathway after ER stress, the transcription factor ATF4 is specifically induced. ATF4 is constitutively transcribed in nonstressed cells, even though its transcripts cannot be efficiently translated due to the presence of short open reading frames (5′-ORF) in its 5′-untranslated region (5′-UTR) that interferes with initiation at the proper start codon. During ER stress, these short ORFs are no longer utilized which leads to a dramatic increase in ATF4 protein (10, 39). IRE1 is a transmembrane serine/threonine protein kinase and has intrinsic endoribonuclease (RNase) activity. Upon activation of the UPR, the RNase domain of IRE1 is activated and this leads to removal of a 26-nucleotide intron from X-box binding protein 1 (XBP1) mRNA. The splicing causes a translational frameshift, generating a potent transcriptional activator of mammalian unfolded protein response elements (UPRE) (4, 41, 51). Although the full complement of genes activated in response to XBP1 splicing has not been identified, these genes include the ER mannosidase EDEM, which is involved in the degradation of nascent misfolded ER glycoproteins (ER-associated degradation, ERAD). Therefore, the machineries of ERAD are considered to be upregulated downstream of the IRE1-XBP1 pathway (52).

ATF6, a membrane-bound transcription factor, is a type II transmembrane protein, and contains a basic leucine zipper (bZIP) domain in its cytoplasmic region. After ER stress, ATF6 is processed by regulated intramembrane proteolysis (RIP), and the cleaved cytoplasmic region of ATF6 liberated from the membrane is translocated into the nucleus. Here it functions as an active transcription factor designated pATF6(N) via direct binding to the CCACG sequence of the ER stress response element (ERSE), when the general transcription factor NF-Y also binds to the CCAAT sequence of the ERSE (37, 49, 50). The resultant activation of ERSE induces transcription of the target genes including ER molecular chaperones and XBP1.

Recently, researchers identified several new members of the membrane-bound transcription factor family that are structurally similar to ATF6. These new members, including OASIS (17), Luman (34), Tisp40/AIbZIP (1, 24), and CREBH (53), all possess a transcription activation domain, a bZIP domain in close proximity to a hydrophobic transmembrane domain, and a domain that resides in the ER lumen. These may be relevant to the cell type-specific ER stress responses as their distributions are not ubiquitous but instead are highly unique.

A NOVEL ER STRESS TRANSDUCER, OASIS

OASIS is a novel ER stress transducer specifically expressed in astrocytes

Among the cell populations in the nervous system, which is composed of heterogeneous cells including neuronal and glial cells, astrocytes have the unique ability of being able to tolerate and even proliferate under ischemic and hypoxic stress conditions that lead to ER stress (31). This phenomenon raises the possibility that astrocytes could adapt to ER stress using different signaling pathways from those of neurons or other cells; that is to say, there could be astrocyte-specific molecules that modulate the UPR pathway.

The OASIS gene was identified originally as a gene specifically induced in long-term cultured astrocytes (12, 30). OASIS is a member of the CREB/ATF family and contains a bZIP domain in its cytoplasmic region. Human OASIS contains 519 amino acids, and has a predicted type II transmembrane topology (Fig. 1A). Its N-terminus containing the transmembrane domain is 31% identical to ATF6, but its C-terminus, the portion which is within the ER lumen, does not show homology to ATF6. Figure 1B compares the sequences of human OASIS, ATF6, and the sterol regulatory element binding protein-2 (SREBP-2) in their transmembrane domains and in the immediately surrounding regions. In the luminal segment, OASIS contains the sequence RSLL (beginning at residue 423), which fits the RxxL consensus for S1P, a membrane-anchored serine protease whose active site faces the Golgi lumen (6, 38). Indeed, OASIS is cleaved at the transmembrane region in response to ER stress in astrocyte-derived C6 glioma cells (Fig. 1C). Mutation in the RSLL sequence inhibits the cleavage, and overexpression of S1P and S2P results in acceleration of the cleavage during

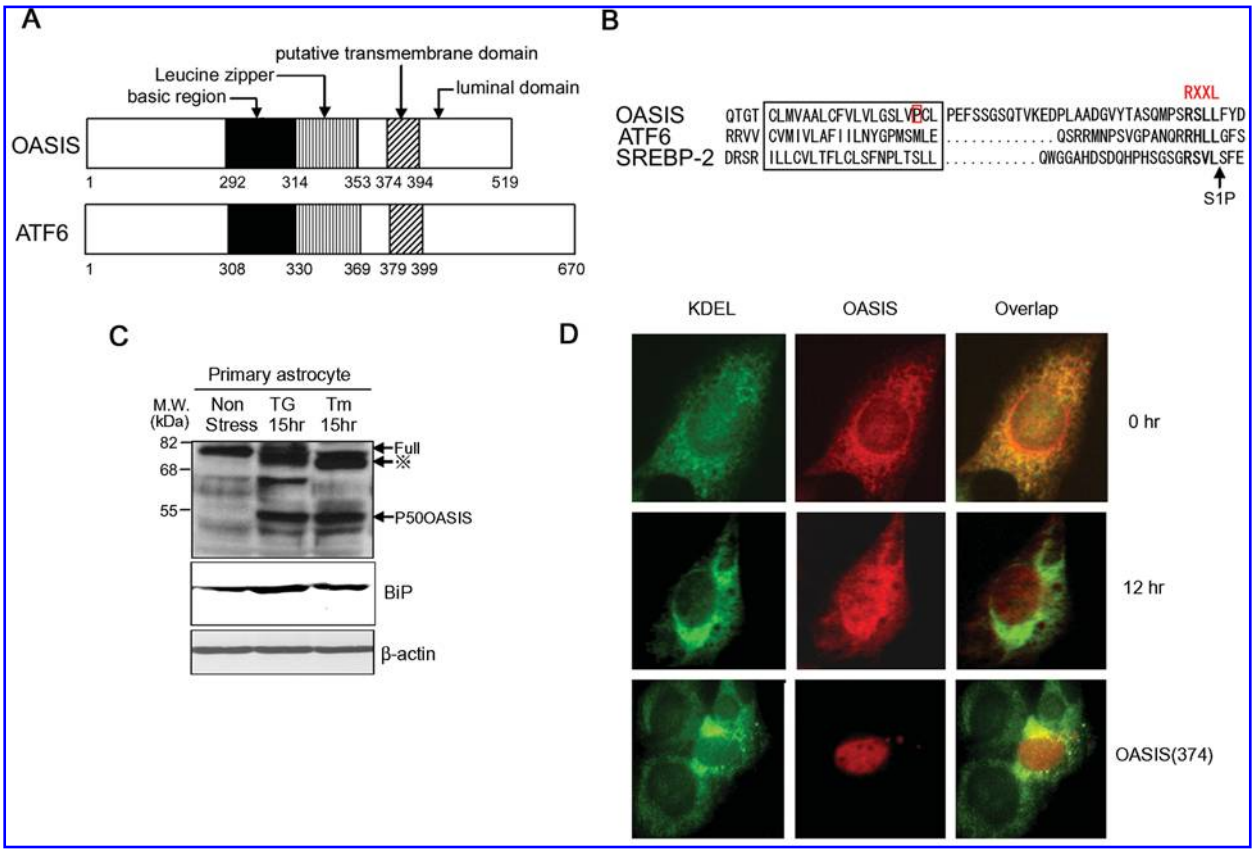

FIG. 1. OASIS is upregulated and cleaved at the transmembrane region in response to ER stress in astrocytes. (**A**) Predicted peptide features of human OASIS and ATF6. The basic region, leucine-zipper, putative transmembrane domain, and luminal domain are indicated. (**B**) Comparison of amino acid sequences of transmembrane regions of human OASIS, ATF6, and SREBP-2. Consensus sequence of the S1P site (RxxL; *highlighted in red*) is conserved within these proteins. The proline residue, *boxed in red*, in the transmembrane region of OASIS is a putative S2P recognition site (48). The box denotes the position of the transmembrane domains. (**C**) Expression of endogenous OASIS in primary astrocytes. Cells were incubated with 1 μ*M* thapsigargin (TG) or 3 μg/ml tunicamycin (Tm) for 15 h, and lysates subjected to Western blotting with anti-OASIS antibody. A 50 kDa band (p50OASIS) appears in cells exposed to ER stress. The *asterisk* denotes partially *N*-glycosylated or nonglycosylated forms of OASIS. Anti-KDEL antibody recognizes BiP. (**D**) Subcellular localization of OASIS. C6 glioma cells stably transfected with OASIS were incubated in presence or absence of 1 μ*M* thapsigargin for 12 h, then co-stained with anti-OASIS and anti-KDEL antibodies. Note, OASIS immunoreactivity completely overlaps that of KDEL under normal conditions, but after ER stress, the OASIS signal accumulates in the nucleus. *Lower panel* shows OASIS (374), which is C-terminal deletion mutant, localized in the nucleus.

ER stress (23). Thus, OASIS is cleaved by S1P and S2P in response to ER stress, similarly to the case of ATF6. Under normal conditions, OASIS localizes in the ER membrane (Fig. 1D). When cells are treated with ER stressors, cleaved fragments of OASIS (p50OASIS) translocates into the nucleus.

ATF6 contains a stretch of amino acid sequence in its luminal domain that is significant for translocation from the ER to the Golgi apparatus (42). All deletion mutants for the luminal domain of OASIS, however, show that proteolytic processing and translocation to the Golgi apparatus remain intact, indicating that OASIS does not have sequences significant for Golgi localization signaling. Therefore, there could be other systems for translocation of OASIS to the Golgi apparatus in response to ER stress. Moreover, interaction of the lumenal domain of OASIS with the molecular chaperone BiP has not been detected, thus it is unclear whether OASIS can sense the accumulation of unfolded proteins in the ER.

OASIS is transcriptionally induced after ER stress in astrocytes

A relatively low level of OASIS mRNA expression is detected before ER stress. This signal increases at 6 h after ER stress and a higher level of expression is observed at 12 h. The temporal changes in OASIS mRNA expression during ER stress match the expression patterns of BiP mRNA, a well-known target gene for the UPR. In contrast, the stresses that do not activate the UPR, cannot induce the expression of OASIS mRNA; indicating that the induction of OASIS transcript may be regulated under UPR signaling.

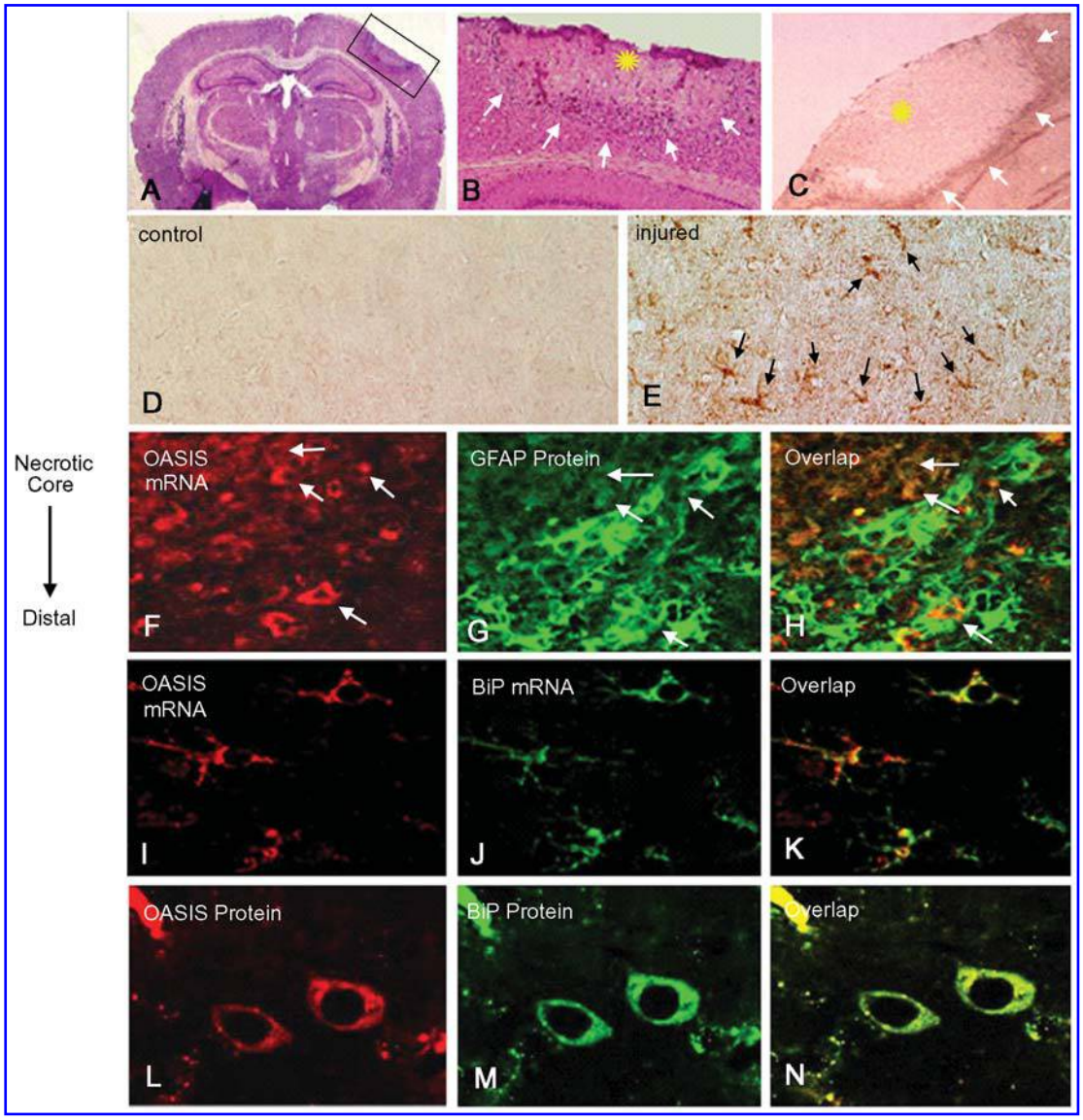

FIG. 2. OASIS expression after cryo-injury to the cortex. Photomicrograph of cryo-injured mouse brain (H.E. stain, 7 days after the injury). The cryo-injury was inflicted to the right cerebral cortex. (**B**) A higher magnification of the *boxed area* in (**A**) is shown. The lesion reproducibly consists of a necrotic core region (*star*) and a surrounding reactive region (*arrows*). (**C**) In situ hybridization histochemistry of OASIS mRNA. OASIS mRNA (*arrows*) is detected in the region surrounding the necrotic lesion (*star*). (**D,E**) Immunohistochemistry of OASIS in control (**D**) and injured (**E**) brain. Note that OASIS is expressed in reactive astrocytes in the injured region (*arrows*). (**F–H**) Combined in situ hybridization and immunohistochemistry analyses of OASIS mRNA and GFAP protein. OASIS mRNA expression is primarily observed in cells close to the necrotic core. These cells have a moderate level of GFAP-like immunoreactivity (proximal reactive astrocytes (35)). *Arrows* show cells that are double-labeled for OASIS mRNA and GFAP protein. In contrast, cells distant from the necrotic core show intense immunoreactivity for GFAP and prominent cellular processes (distal reactive astrocytes), and are mostly negative for OASIS mRNA. (**I–K**) Double-labeling in situ hybridization for OASIS and BiP mRNAs in injured brain. (**L–N**) Double-labeling immunohistochemistry for OASIS and BiP proteins. OASIS immunoreactivity is primarily detected in the cytoplasm and overlaps strikingly with BiP immunoreactivity.

Interestingly, in non-glial cells such as neuroblastoma SK-N-SH cells, HEK293T cells, and mouse embryonic fibroblasts (MEF), expression of OASIS mRNA is at an extremely low level, or the expression is gradually reduced after ER stress. Thus, OASIS is specifically induced in astrocytes in response to ER stress.

In brain injury, reactive astrocytes express OASIS mRNA (12, 27). OASIS mRNA is significantly induced in the cells surrounding the necrotic tissue 7 days after injury, having a similar distribution to that of glial fibrillary acidic protein (GFAP)-like immunoreactivity (Fig. 2). The expression patterns suggest that cells expressing OASIS mRNA are

proximal reactive astrocytes with weak GFAP immunoreactivity (35). On the other hand, distal reactive astrocytes, with intense GFAP immunoreactivity and prominent cellular processes, are negative for OASIS mRNA. Taken together, these results suggest that in the central nervous system, the transcription of OASIS is induced in astrocytes following brain injury.

OASIS acts on both CRE and ERSE in the BiP promoter

The N-terminal portion of OASIS with the bZIP domain translocates into the nucleus in response to ER stress. What are the targets of OASIS? The promoter of the ER molecular chaperone, BiP, contains a cyclic AMP response element (CRE) and three tandem ERSEs. BiP is induced during ER stress, even in astrocytes, thus BiP may be one of the targets of OASIS. Treatment of glioma cell lines with OASIS small interfering RNA (siRNA) significantly suppresses the induction of BiP mRNA after ER stress. In addition, overexpression of the OASIS N-terminal fragment increases the reporter activities of BiP promoter containing both CRE and ERSEs. Therefore, OASIS has the potential to induce BiP mRNA. Mutations in the CRE or ERSE sites reduce the activities of the BiP reporter by ~50% or 20%, respectively, indicating that OASIS acts as a transcriptional activator at both elements, but preferentially acts at the CRE site.

The majority of the CREB/ATF family members have been demonstrated to form heterodimers with a variety of bZIP proteins. Indeed, ATF4 and ATF6 have been reported to form heterodimers with Fos, Jun, and C/EBP, and CREB-RP (ATF6β), respectively (8, 33). OASIS also forms heterodimers with ATF6 N-terminal fragments and the formation of this heterodimer synergistically transactivates the ERSE reporter.

Apoptosis induced by ER stress is suppressed by OASIS

BiP is well known to function as a cytoprotective protein in stressed cells (19, 43). As OASIS induces the expression of BiP mRNA during ER stress, OASIS might protect cells from ER stress; and indeed, OASIS-transfected cells are significantly more resistant to ER stress-induced cell death (Fig. 3). Alternatively, reduction of the levels of OASIS by RNA interference results in promotion of cell death induced by ER stress, but does not affect cell death induced by staurosporine. Taken together, these results show that OASIS is required for cell survival after ER stress in astrocytes; though the detailed mechanisms by which OASIS plays this important role remain unclear. However, the findings of decreased BiP induction after ER stress in cells treated with OASIS siRNA raise the possibility that activation of the UPR including induction of molecular chaperones by OASIS is involved in resistance to ER stress in astrocytes. The other possibility is that OASIS may transcriptionally upregulate anti-apoptotic genes that could suppress cell death. It is important that target genes induced by OASIS are identified to clarify the precise mechanisms of resistance to ER stress in astrocytes. Putative mechanisms for the activation of the UPR by OASIS in astrocytes are shown in Fig. 3D.

OASIS may regulate the UPR in a cell-specific manner

The expression pattern of the OASIS gene has been investigated in developing mouse embryos by in situ hybridization histochemistry, and is reported to be expressed in preosteoblasts of the ribs, alveolar bone, and tooth bud, suggesting that OASIS may be involved in osteogenesis and skeletal development (12, 27). Interestingly, the expression patterns of OASIS are strikingly similar to those of XBP1, which has been known to be induced by ER stress at the transcriptional level in various cell types throughout skeletal development. Preosteoblasts are major sources of synthesis and secretion of collagen to form bones; augmentation of the folding capacity in the ER must therefore be important for quality control of secreted collagen produced in large amounts. This idea raises the possibility that UPR signals mediated by both the OASIS and IRE1-XBP1 pathways might be activated in preosteoblasts at the skeletal development stage, to deal with the large amounts of collagen needing to be correctly folded and secreted. As described above, OASIS is induced in response to ER stress in cultured astrocytes; it also appears to be upregulated in other types of cells in response to ER stress caused by cell type-specific environments relevant to development, differentiation and aging.

NEW MEMBERS OF THE MEMBRANE-BOUND TRANSCRIPTION FACTOR FAMILY STRUCTURALLY SIMILAR TO ATF6

In humans, there are more than 55 known bZIP transcription factors (26). By sequence similarity in the coiled-coil region, these bZIP transcription factors can be divided into 16 different families. OASIS, CREBH, AIbZIP/Tisp40, and Luman are identified as members of the OASIS family (Fig. 4). OASIS family members are Type II transmembrane proteins and are localized in the ER. Some OASIS family proteins are reported to act as novel ER stress transducers and play a role in UPR subpathways. CREBH is identified as a hepatocyte-specific bZIP transcription factor belonging to the CREB/ATF family (29). In response to ER stress, CREBH is cleaved by RIP and is required to activate expression of acute phase response genes, including serum amyloid P-component and C-reactive protein (53). AIbZIP/Tisp40, specifically expressed in prostate/testis, is cleaved by RIP and has the capacity to activate promoter elements of UPR genes (1, 24). Although Luman is also cleaved by RIP, Luman cannot be activated in response to ER stressors such as tunicamycin and thapsigargin. However, overexpression of Luman stimulates transcription of EDEM, a key molecule for ER-associated degradation, suggesting that Luman may have a pathway different from that of the common ER stress response (5, 34).

CREBH knockdown mice embryos and AIbZIP/Tisp40 deficient mice have already been reported. The histopathological analysis of the CREBH knockdown embryos at E14.5 did not reveal any morphological or developmental defects, and the AIbZIP/Tisp40 deficient mice were born at expected

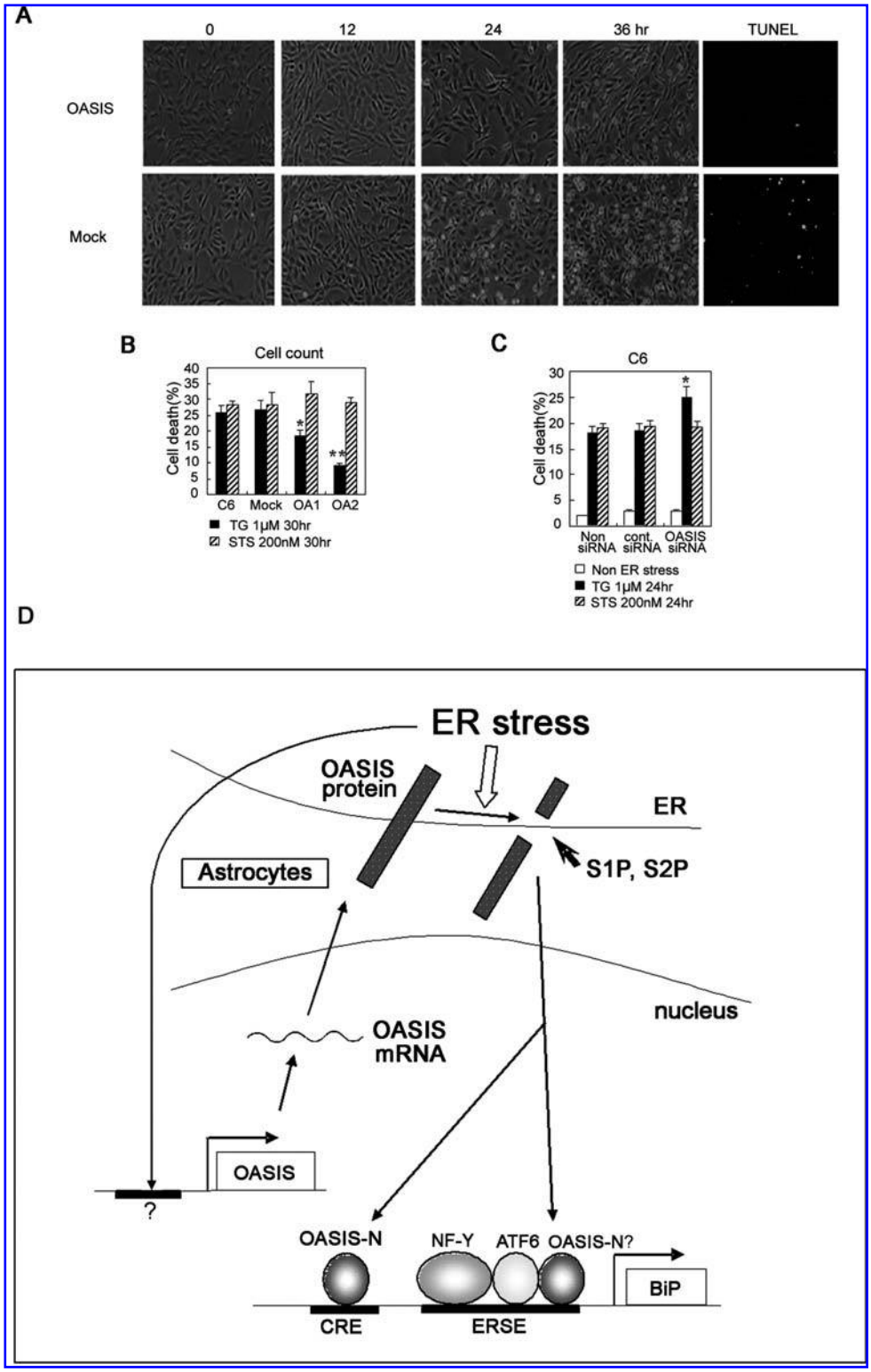

FIG. 3. Protective effects of OASIS on ER stress-induced cell death. (**A**) Representative phase-contrast micrographs of mock and OASIS-expressing cells are shown. Cells were exposed to 1 μ*M* thapsigargin for the indicated periods. The *right panels* show TUNEL staining 36 h after the treatment. In cells expressing OASIS, cell death is delayed and suppressed compared with mock vector-transfected cells. (**B**) Quantitative analysis of cell death at 30 h after treatment with thapsigargin or staurosporine. Cell death was determined by the morphology (round and shrunken cells were counted as dead cells). Data are the means ± S.D. of the results of four independent experiments. $*p < 0.05$, $**p < 0.01$ relative to the control (Student's *t*-test). (**C**) Cell death assay of C6 glioma cells treated with OASIS siRNA. Cells were treated with thapsigargin or staurosporine for 24 h. (**D**) Putative mechanisms responsible for activation of the UPR by OASIS in astrocytes. OASIS is induced at the transcriptional level during ER stress in astrocytes. Translated OASIS is cleaved at the membrane by S1P and S2P in response to ER stress, and its cleaved N-terminal cytoplasmic domain translocates into the nucleus; and then activates transcription of target genes by acting at the CRE and ERSE sites. This signaling pathway mediated by OASIS may contribute to cell survival after ER stress in astrocytes.

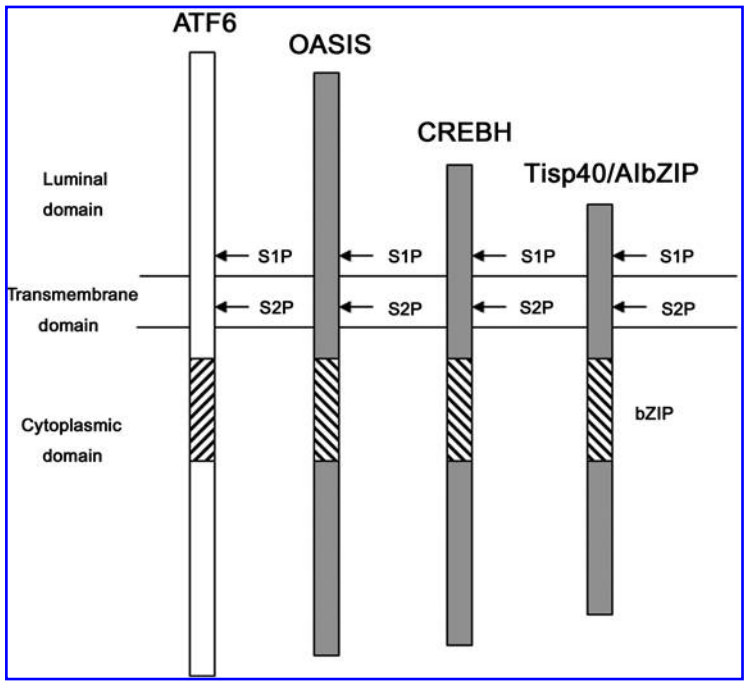

FIG. 4. Structures of membrane-bound transcription factors homologous to ATF6 and OASIS.

ratios, were healthy, and displayed normal long-term survival rates. However, although the seminiferous tubules of AIbZIP/ Tisp40-deficient mice contained all of the developmental stages, there was evidence for increased apoptosis of meiotic/ postmeiotic germ cells (1). Thus, the phenotypes of mice deficient in proteins of the OASIS family are milder than those of mice deficient in major ER stress transducers. These recent studies could indicate that proteins of the OASIS family play an auxiliary role in the major ER stress transducer pathway.

CONCLUSION

In this review, we introduced the structure and functions of OASIS, a transmembrane bZIP transcription factor, and concluded that OASIS is a novel ER stress transducer that regulates UPR signaling in astrocytes. Astrocytes have a potential to protect neurons after brain injury by releasing neurotrophic factors and cytokines. Activation of UPR signaling by OASIS in reactive astrocytes after injury not only leads to the strengthening of astrocytes against cell damage, but also helps to protect neurons from various neuronal insults that induce ER stress, such as ischemia and hypoxia. As discussed, a new group of ER stress transducers including CREBH, AIbZIP/Tisp40 and Luman, has been identified whose members are homologous to OASIS. These transducers are processed in a manner similar to that of OASIS and ATF6, which in response to ER stress are sequestered in cellular membranes and activated by RIP. This process allows cells to respond rapidly to physiological crises by activating pre-made transcription factors. Understanding RIP regulation of these transcription factors and determining the target genes should enable the discovery of novel signaling pathways involved in the UPR or cell type-specific ER stress responses. Further, there is evidence that ER stresses are associated with genetic (7, 21, 32) or neuronal degenerative disorders (13, 15, 28); thus, experimental manipulation of these transcription factors, including OASIS, might allow for the development of therapeutic strategies for ER stress-related diseases.

ACKNOWLEDGMENTS

The authors are grateful to the members of the laboratory who contributed to the experiments described in this review. This work was supported by grants from the JSPS KAKENHI (#17200026), the Sumitomo Foundation, and the Astellas Foundation for Research on Metabolic Disorders.

ABBREVIATIONS

bZIP, basic leucine zipper; CRE, cyclic AMP response element; eIF2α, eukaryotic initiation factor 2α; ER, endoplasmic reticulum; ERAD, ER-associated degradation; ERSE, ER stress response element; RIP, regulated intramembrane proteolysis; S1P, site-1 protease; S2P, site-2 protease; SREBP, sterol regulatory element binding protein; UPR, unfolded protein response UPRE, unfolded protein response element; UTR, untranslated region.

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Address reprint requests to:
Kazunori Imaizumi
Division of Molecular and Cellular Biology
Department of Anatomy, Faculty of Medicine
University of Miyazaki
Kihara 5200, Kiyotake
Miyazaki 889-1692, Japan

E-mail: imaizumi@med.miyazaki-u.ac.jp

Date of submission to ARS central, November 27, 2006; date of acceptance, December 5, 2006.

This article has been cited by:

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