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Minireview Article

What is the Physiological Role of Matrin-3?

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ABSTRACT

In mammals, Matrin-3 is a highly conserved inner nuclear matrix protein of 125 kDa. This protein has been implicated in various functions, including the maintenance of cell viability, proliferation and stemness, DNA protection, mRNA stability and transport of transcripts, and viral assembly as well as involvement in some neurodegenerative diseases. Yet, its physiological mode of action remains elusive. Here, we summarize the main data in the literature on matrin-3's role in cells and suggest that its specific interaction with GRP78, a principal regulator of the unfolding protein pathway (UPR), may shed light on some of the functional activities associated with Matr3.

INTRODUCTION

Matrin-3 (MATR3**),** a highly conserved 125 kDa protein, was first identified as one of the major components in the nuclear matrix from rat liver cells **(**Nakayasu and Berezney, 1991). Matr3 consists of 847 amino acids of which, a large part of the sequence consists of disordered regions, two DNA-binding zin finger (ZF) domains, and two RNA-binding domains (Hibino et al., 2006; Hisada-Ishii et al., 2007). The protein Matrin-3 has been implicated in a variety of cellular functions. First, Matr3 has been involved in the regulation of transcription, mRNA splicing, mRNA stability (Zhang and Carmichael, 2001; Yedavalli and Jang, 2011; Kula et al., 2011), as well as in DNA damage response signaling pathway (Salton et al., 2010). Second, several studies implicated matrin-3 in cell viability and proliferation. In fact, homocysteine-stressed endothelial cells led to the downregulation of Matr3 and reduced proliferation of the endothelial cells (Fuchs et al., 2006). Likewise, the use of siRNA oligonucleotides also resulted in the decrease of Matr3 level, reduced proliferation, and death of the endothelial cells (Przygodzka et al., 2011).

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Moreover, small interfering siRNA-mediated knockdown of matrin-3 resulted in neural differentiation of neural stem cells (Kanako et al., 2018). Similarly, when serine 208 residue of Matrin-3 was point mutated to Ala 208 (Ser208 Ala mutant Matrin-3), or ATM kinase (Ataxia telangiectasia mutated kinase), which phosphorylates Matrin-3 at Serine 208, was inhibited, neuronal differentiation and reduced proliferation of neural stem cells was observed (Kanako et al., 2018). Consistent with this observation of Matrin-3's role in the maintenance of cell proliferation, tributyltin oxide (TBTO)-, an immunosuppressant model compound, treated thymoma cell line led to the downregulation of Matr3 (Osman and van Loveren, 2012). Using immunoprecipitation experiments of lysates obtained from control and tributyltin oxide (TBTO)-treated thymoma cell line (EL4), these latter authors showed that Matr3 specifically interacts with the heat shock proteins GRP 78, glucose-regulated protein (also known as binding immunoglobulin protein, BiP), GRP75 and glutathione S-transferase π isoform 2. Matr3 and its partners were identified by MS/MS analysis and confirmed by immunoblot (Osman and van Loveren, 2014). Of interest is that the heat shock protein GRP78 (one of the identified partners of Matr3) was downregulated in the TBTO-treated cells (Osman and van Loveren, 2014). More recently, the product Lichochalcone H (LCH), which has various pharmacological properties, including antioxidant and anti-inflammatory effects, induced in human oral squamous carcinoma cells, the downregulation of

matrin-3 and reduced proliferation of the cancer cells (Su-hyun et al., 2019).

Third, Matr3 has been involved in the pathogenesis of several neurological disorders. For instance, a decrease in Matr3 level was reported in fetal Down's syndrome brain (Bernert et al., 2002), and a 100-fold decrease of the concentration of Matr3 in plasma umbilical cord was reported for Down syndrome patients, compared to control group (Sui et al., 2014). Also, a missense mutation of a single amino acid in Matr3 was found to cause in humans autosomal-dominant distal myopathy often complicated by the vocal cord and pharyngeal weakness (Senderek et al., 2009), and mutations in the Matr3 gene was associated with the cause of familial amyotrophic lateral sclerosis, a terrible neurodegenerative disease characterized by the progressive paralysis and respiratory failure leading ultimately to death (Johnson et al., 2014).

Although these findings demonstrate the involvement of Matr3 in cell viability and proliferation, in DNA damage pathway, transcription regulation, RNA transport, and has been implicated in some neurodegenerative diseases, the mode of action of Matr3 is unknown. In this perspective minireview, we propose that the interaction of the heat shock proteins GRP78 and GRP75 with Matr3 may explain some of the latter's functional activities and its observed downregulation in cells. Conversely, as suggested before (Osman and van Loveren, 2014), Matr3 might assist GRP78 in binding with DNA and thus provide a distinct nuclear mechanism for the previously suggested GRP78's role in genome repair (Zhai et al., 2005).

Role of Matrin-3 in cell proliferation, stemness and DNA protection

Although much effort has been made in the study of the functional role of matrin-3, as described in the introductory section, the mode of action of this protein remains yet to be unveiled. For instance, how does Matr3 support the maintenance of cell proliferation and stemness? We argue that the answer might be found in the interaction of Matr3 with other protein partners. One of the salient characteristics of Matr3 is that its primary structure consists mostly of internally disordered regions. Recent developments in the field of protein structures show that such internally disordered regions of proteins, though devoid of three-dimensional structure, are highly likely functionally relevant (e.g., binding with other proteins, sites for posttranslational modifications) (Van der Lee et al., 2014). Approaches such as computational analysis of these internally disorganized regions and their functional characterization combined with other analytical techniques, like proteomics, and co-immunoprecipitation procedures may give insights into the functions of the internally disordered regions of Matr3; and, therefore, predict and reveal the different partners with which Matr3 interacts and their mode of binding. Indeed, some of these approaches and other analytical techniques have already provided some clues and insights into matrin-3's functions. Proteomics, immunoprecipitation methods, genetic approaches, and other analytical tools have revealed the implication of matrin-3 in neurodegenerative diseases, in the maintenance of cell proliferation, and renewal as well as the interaction of matrin-3 with other protein partners (Coelho et al., 2016). As mentioned above, the combination of proteomics and immunoblot analyses revealed that Matr3 specifically interacted with the heat shock proteins glucose regulated protein GRP78, GRP75 and glutathione S-transferase π isoform 2 (GSTπ 2) (Osman and van Loveren, 2014). The interaction of Matr3 with these proteins might facilitate some of the reported cellular activities of Matr3, such as cell viability and proliferation. GRP78 is the master regulator of the unfolded protein response signaling pathway (UPR), which monitors and regulates protein-folding homeostasis. In addition to this protein quality control role, recent advances have shown that this GRP78 chaperone promotes proliferation and stemness of both normal and cancer cells. For instance, a recent report has shown that GRP78 is responsible for the stemness and renewal features of pancreatic cancer cells (Dauer et al., 2019). In fact, the downregulation of GRP78 reduced clonogenicity and renewal properties of these pancreatic cancer cells (Dauer et al., 2019). Consistent with the role of GRP78 in cell survival is the report that an acute deficiency of GRP78 in adult hematopoietic stem cells (HSCs) (following knock out of mouse model adult, deleting the Grp78 gene) resulted in a significant reduction of HSC pool (i.e., reduction of common lymphoid and myeloid progenitors in the mutant mice) (Wey et al., 2012). This study indicates that the crucial role of GRP78 in cellular homeostasis, survival and maintenance is not limited to cancer cells.

Another important role of GRP78 is its protective role against UV-induced DNA image (Zhai et al., 2005). Both heat shock proteins GRP78 and GRP75 are known to be localized not only in the cytoplasm but also in the nucleus (Bhattacharyya et al., 1995; Zhang and Lee, 2011). The nuclear GRP78 was suggested to participate in DNA repair because knockdown of this chaperone in human RSa cells sensitized these cells to UV-induced cell death principally due to damaged DNA repair (Zhai et al., 2005). The mechanism of GRP78 interaction with DNA is not known (Zhai et al., 2005).

Table 1. The downregulation of matrin-3 results in reduced cell proliferation and stemness

Cell-type	Nature of the chemical agent incubated in the cells	Effect on Matr3 level	Effect on cell growth	Reference
Endothelial cells	Homocysteine	Downregulation	Reduced proliferation	Fuchs et al., 2006
Endothelial cells	SiRNA oligonucleotides	Knockout	Reduced proliferation	Przygodzka et al., 2011
Neural Stem Cells	Si-RNA knockdown-mediated down of Matr3; Transinfection Ser 208 Ala mutant Matr3; Inhibition of ATM kinase (Ataxia telangiectasia mutated kinase)	Knockout	Neuronal differentiation of stem cells in vitro; reduced proliferation of stem cells	Kanako et al., 2018
Thymoma cells (EL4) cell line	Tributyltin oxide (TBTO)	Downregulation	Reduced proliferation	Osman and van Loveren, 2012; 2014
Human oral squamous cell carcinoma	Licochalcone (LCH)	Downregulation	Reduced proliferation	Su-hyun et al., 2019

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Downregulation of Matr3

Another relevant aspect of Matr3 is to explain the underlying mechanism of its observed downregulation in various studies (Table 1). One might ask: What is the pathway leading to the downregulation of matrin-3? Is this downregulation of the protein controlled at the transcription level or is it due to protein degradation? This downregulation of Matr3 seems to be not at the protein synthesis level because one of the previous studies clearly showed that changes in the level of mRNA was opposite to the protein level changes, i.e., an increase in the mRNA level corresponded to a decrease in the protein level (Fuchs et al., 2006). Thus, the downregulation of Matr3 appears to be due to protein degradation. This downregulation of Matr3 seems to be mediated by caspase activities. There is some evidence for that. First, in vitro characterization of CaM-binding motif and caspase cleavage site on matrin-3 and in vitro cleavage of Matr3 by caspase activities was reported before (Valencia et al., 2007). Second, this is consistent with the observed caspase-mediated degradation of Matr3 in TBTO-treated thymoma cell line (Osman and van Loveren, 2014) and the immune-cytological evidence of TBTO-induced caspase-3 activation reported in Jurkat cells (Katika et al., 2012). The question then is: what may trigger this caspase activity (s)? Again, the chaperone GRP78 may be involved in this caspase-mediated degradation of Matr3. Indeed, GRP78 was downregulated in the above-described TBTO-treated thymoma cell line compared to control cells (see figure 4A in the reference Osman and van Loveren, 2014). It is known that GRP78 binds with caspase 7 and that the downregulation of GRP78 leads to the release and activation of caspase7 (Reddy et al., 2003). Therefore, it is tempting to suggest that the downregulation of GRP78 in the examined tissues may trigger the release of caspase7 and, consequently, caspase-mediated degradation of Matrin-3, thus explaining the observed downregulation of matrin-3 in the reported various studies (Table 1).

Matrin-3 and neurodegenerative diseases

Matr3 is associated with some neurodegenerative disorders. Some of these disorders are due to point mutations of Matr3 (Senderek et al., 2009; Johnson et al., 2014), and in some diseases, like Down syndrome, the protein is downregulated (Bernert et al., 2002; Sui et al., 2014). There is accumulating experimental evidence that makes the unfolding protein response pathway (UPR) implicated in neurogenerative diseases (Katayama et al., 1999; Baek et al., 2019]. This involvement is not surprising because a salient feature of these neurological degenerative diseases is the accumulation of misfolded specific proteins (Katayama et al., 1999; Baek et al., 2019). The master regulator of UPR pathway is GRP78. Of interest is the observation that a lower expression level of GRP78 has been evidenced in the brains of Alzheimer's and Parkinson's disease patients (Katayama et al., 1999; Baek et al., 2019). In a recent study, using a quantitative western blot technique, a significant decrease in the level of GRP 78 was reported in various regions of the brain of post-mortem PD patients (Baek et al., 2019). Whether this decrease of GRP78 level reflects a dysfunctionality of the UPR pathway, and, therefore, acts as the primary event, or whether this decrease of the protein level is a consequence of an antecedent neuronal event is not yet clear. Nevertheless, as discussed above, the decreased expression of GRP78 level in tissues might lead to the downregulation of Matr3. Once again, pointing a potential link between malfunctioning of the UPR pathway and the involvement of Matr3 in some neurodegenerative diseases.

Finally, Matr3 is a phosphoprotein, which means that, under certain conditions, this protein can be in a phosphorylated form. In mammals, two kinases that phosphorylate Matr3 were identified: cAMP dependent protein A (protein kinase A, PKA) and ataxia telangiectasia mutated kinase (nuclear ATM kinase). Activation of NMDA (N-methyl-D-Aspartate) receptor caused cAMP dependent activation of protein kinase A, which was found to phosphorylate Matr3 at Ser188 in cerebellar neurons in culture, resulted in its degradation (Giordano et al., 2005). Inhibition of PKA prevented the NMDA induced phosphorylation of Matr3, and consequently, its degradation. How this phosphorylation of Matr3 leads to its degradation is obscure. The phosphorylation modification may induce a conformational change in the protein, which leads to its degradation. The other kinase that acts on Matr3 is the nuclear ATM kinase, which phosphorylates Matr3 at Ser208. This ATM dependent phosphorylation of Matr3 at S208 is stimulated by FGF2 in fibroblast cells. The phosphorylation of Matr3 at S208 promoted the stemness of the neural stem cells both in vitro and in vivo (Kanako et al., 2018). But the question is: how does this ATM kinase-dependent phosphorylation of Mar3 promote the stemness of the neural stem cells? In sum, it should be noted that there are other identified phosphorylation sites of Matr3, whose physiological roles and the kinases responsible for their catalysis remain unknown (Beausoleil et al., 2004).

CONCLUSION

In conclusion, this perspective review highlighted and summarized the role of matrin-3 in cells. As reported earlier (Osman and van Loveren, 2014], Matr3 interacts specifically with some proteins, including GRP78, the master regulator of the UPR pathway. Matr3 plays a role in DNA protection and promotes cell proliferation and stemness, but the mode of action of Matr3 regarding these activities remain elusive. Interestingly, as discussed in this review, accumulating experimental evidence shows that GRP78 supports cell proliferation and renewal properties in both cancer and normal cells. Hence, we propose that the interaction of the proteins GRP78 and Matr3 may assist in their cellular functions. As suggested before (Osman and van Loveren, 2014), Matr3 might assist GRP78 in binding with DNA as Matr3 has binding domain sites for DNA. This interaction of the two proteins would provide a mechanism of interaction between DNA and GRP78. GRP78 has been implicated in DNA damage repair though the underlying mechanism for their interaction is not known (Zhai et al., 2005). On the other hand, data in the literature support that matrin-3 seems to be implicated in DNA damage response pathway (DDR). The central regulators of the DDR pathway are ATM and ATR kinases. Matr3 is a target of the nuclear ATM kinase. The unfolding protein response pathway (UPR) and the DNA damage response pathway are intertwined and are for survival and against cellular insults (Dicks et al., 2015). Thus, there seems to be crosstalk between the two pathways, and that GRP78 and Matr3 appear to play a role in this crosstalk. To better understand the physiological role of Matr3, the interaction of this protein with other partners must be thoroughly investigated. Therefore, to achieve more insights and a comprehensive view of the functional role of Matr3, we need to combine computational analysis of the intrinsically disordered sequences of this protein with analytical approaches such as proteomics, co-immunoprecipitation, and genetic manipulations, etc. T he functional characterizat- ion of these disordered sequences of Matr3 might allow us to identify potential sites for post-translational modifications and potential protein partners of matrin-3. The identification of sequences in Matr3 that bind with the known partners

like the proteins described in this review would lend support to the ideas expressed here.

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