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Arsenic Exposure and Compromised Protein Quality Control

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Abstract

Exposure to arsenic in contaminated drinking water is a worldwide public health problem that affects more than 200 million people. Protein quality control constitutes an evolutionarily conserved mechanism for promoting proper folding of proteins, refolding of misfolded proteins, and removal of aggregated proteins, thereby maintaining homeostasis of the proteome (i.e., proteostasis). Accumulating lines of evidence from epidemiological and laboratory studies revealed that chronic exposure to inorganic arsenic species can elicit proteinopathies that contribute to neurodegenerative disorders, cancer, and type II diabetes. Here, we review the effects of arsenic exposure on perturbing various elements of the proteostasis network, including mitochondrial homeostasis, molecular chaperones, inflammatory response, ubiquitinproteasome system, autophagy, as well as asymmetric segregation and axonal transport of misfolded proteins. We also discuss arsenic-induced disruptions of post-translational modifications of proteins, for example, ubiquitination, and their implications in proteostasis. Together, studies in the past few decades support that disruption of protein quality control may constitute an important mechanism underlying the arsenic-induced toxicity.

Graphical Abstract

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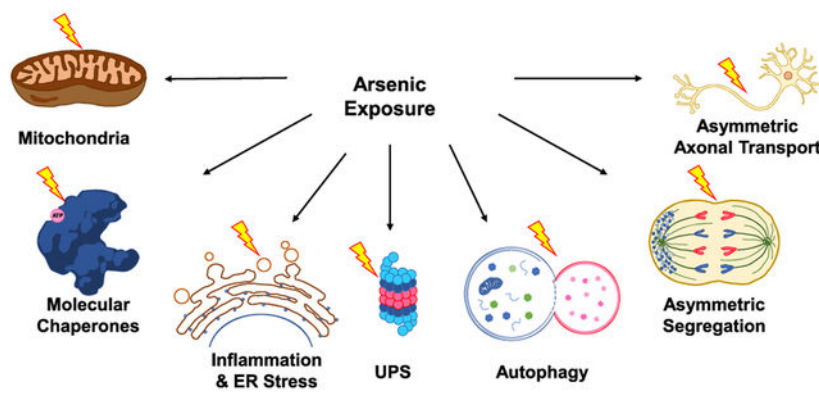
1. INTRODUCTION

Natural occurrence and anthropogenic activities render arsenic species ubiquitously present in the environment.[1] Arsenic contamination in drinking water is a major public health concern in the modern world, where exposure to inorganic arsenic (iAs) in contaminated drinking water or agricultural products impacts approximately 200 million people in over 70 nations.[1] Along this line, exposure to arsenic is thought to contribute to the etiology of many human diseases, including cancer,[2,3] neurodegenerative diseases,[4,5] and type II diabetes.[6,7] Multiple mechanisms are thought to contribute to arsenic-elicited human diseases including binding to cysteine sulfhydryl groups in proteins, induction of reactive oxygen species, disruption of DNA repair, and perturbation of epigenetic pathways of gene regulation, etc.[3,8,9]

In cells, proteins need to be properly folded into their native three-dimensional structures so as to execute their biological functions. This is a challenging task, especially in the context that numerous nascently synthesized polypeptides must fold properly in crowded intracellular environment and they must maintain appropriate folding under a wide range of physiological and environmental stress conditions.[10–12] To maintain homeostasis of the proteome (i.e., proteostasis), cells are equipped with sophisticated, yet highly conserved protein quality control machineries, collectively known as the proteostasis network.[10,11]

Proteostasis network comprises cellular machineries regulating the production, folding, trafficking, degradation, and clearance of proteins.[10,11] In this vein, approximately 30% of proteins in higher eukaryotes possess extensive intrinsically unstructured regions (>30 amino acids in length), which render these proteins metastable and toxic upon aggregation.[13] Therefore, a robust proteostasis network is particularly critical for maintaining correct folding and minimizing aggregation of proteins.

2. METABOLIC TRANSFORMATIONS OF ARSENIC SPECIES

Toxicity of inorganic arsenic (iAs), in both trivalent (iAs^{3+}) and pentavalent (iAs^{5+}) states, in mammals depends largely on their metabolic transformations. The majority of ingested iAs (As^{3+} or As^{5+}) is absorbed by the gastrointestinal tract.[14] In liver, As^{5+} can be reduced by glutathione (GSH) to yield iAs^{3+}, which can undergo iterative oxidative methylation,

catalyzed by arsenite methyltransferase (As3MT), and GSH-mediated reduction to yield organic arsenic species, including monomethylarsonic acid (MMA^V), monomethylarsonous acid (MMA^{III}), dimethylarsinic acid (DMA^V), and dimethylarsinous acid (DMA^{III}).[15] The different chemical forms of arsenic exhibit variations in cellular uptake, efflux, and retention.[16–18] For instance, higher cytotoxicity of MMA^{III} and DMA^{III} over iAs^{3+} is associated with greater cellular uptake and retention of the methylated arsenic species.[16] As a result, it is important to consider both inorganic arsenic species and their methylated metabolites when considering arsenic toxicity.

3. ARSENIC-INDUCED DISRUPTION OF PROTEOSTASIS NETWORK

Chronic exposure to arsenic species was shown to induce aberrant folding and aggregation of proteins,[19,20] which may overwhelm the capacity of proteostasis network and engender a self-propagating, vicious cycle of proteotoxic stress. In the following sections, we review the various protein quality control machineries that can be disrupted in cells upon arsenic exposure (Figure 1).

3.1. Mitochondrial Homeostasis.

Mitochondria are critical organelles in cellular proteostasis owing to their multiple roles in cellular physiology and in shaping cellular decisions for life or death.[21] Mitochondria are important sources of intracellular reactive oxygen species (ROS).[22,23] Given the detrimental effects of oxidative stress on proteostasis, mitochondrial homeostasis is intimately linked with the proteostasis network,[21] as manifested by the observations of mitochondrial dysfunctions in human diseases associated with proteotoxic stress including cancer and neurodegenerative diseases.[24]

Growing lines of evidence from epidemiological, animal, and cellular studies revealed that exposure to iAs can result in mitochondrial dysfunctions,[25–28] which can occur via (i) mitochondrial DNA damage,[25,26,29] (ii) uncoupling of mitochondrial respiration through metabolic reprogramming,[27,30,31] (iii) excessive production of ROS,[25,28,32] and(iv) augmented proton leak from ROS-induced depolarization and damage of mitochondrial membrane (Table 1).[27]

Multiple studies documented that exposure to iAs^{3+} could elicit mitochondrial DNA damage, which could be alleviated by treating cells with an oxygen radical scavenger.[25,26,29] Arsenite was shown to augment glycolysis, diminish the function of electron transport chain, and disrupt pyruvate metabolism in nematodes and human cells.[27,30] This so-called Warburg-like effect may originate from inhibition of mitochondrial metabolic enzymes, for example, pyruvate dehydrogenase, through arsenite-induced ROS.[33] The arsenate-mediated impairment of oxidative phosphorylation may also stem, in part, from the formation of ADP-arsenate.[34]

Trivalent arsenicals were shown to trigger the production of mitochondrial ROS in human cells and *Caenorhabditis elegans* by uncoupling mitochondrial respiration and eliciting mitochondrial dysfunction including altered metabolism, diminished intracellular ATP, and increased proton leak.[27,30] In this vein, As^{3+} exposure was shown to lead to reduced steady-

state ATP levels in cells, partly through the aforementioned disruption of pyruvate metabolism.[27,33]

Several rodent studies indicated that subchronic and chronic exposure to arsenite (i.e., 1–3 months) reduced the activities of mitochondrial antioxidant enzymes, decreased intracellular glutathione level, and augmented lipid peroxidation and protein oxidation.[35,36] This suggests that arsenite exposure triggers oxidative stress, which inactivates mitochondrial enzymes[35] and damages mitochondrial membrane via protein oxidation and lipid peroxidation,[36,37] thereby inducing proton leak.[27]

Apart from enzyme inhibition and membrane damage in mitochondria, chronic (i.e., 90 days) exposure to low concentration of arsenite elicits a dose-dependent elevation in expression of mitochondrial transcription factor A (mtTFA) in RWPE-1 cells.[38] This mtTFA-mediated alteration in mitochondrial signaling, which is believed to arise from arsenic-elicited oxidative stress, leads to mitochondrial DNA damage and elevated levels of mitochondrial ROS while enhancing the survival of cells under proteotoxic stress.[38]

Lastly, mitochondria are interconnected with other components of the protein quality control (PQC) systems.[21]

3.2. Molecular Chaperones.

Molecular chaperones are key modulators of the proteostasis network by sensing and proof-reading misfolded polypeptides to prevent misfolded proteins from aggregation and to actively refold non-native structural ensembles into their correct folding state.[39] This chaperone network is also involved in triage decisions of misfolded proteins for *de novo* folding, refolding, or sorting to other PQC machineries.[40]

Exposure to trivalent arsenic has been shown to disrupt the functions of molecular chaperones.[41] This may proceed through: (i) interfering with the binding of chaperone proteins with their substrates[42] and (ii) disrupting the activities of ATP-dependent chaperones through inhibition of ATP production in mitochondria (Table 1).[43]

As part of the cellular stress response, iAs^{3+} was found to induce the expression of chaperone proteins, especially heat shock proteins HSP70 and sHSPs.[44–46] Additionally, chronic arsenite exposure was shown to up-regulate heat shock proteins via activation of DAF-16/FOXO transcription factor through oxidative stress.[47]

Exposure to iAs^{3+} was observed to suppress protein folding and stimulate the formation of protein aggregates in yeast cells.[41] iAs^{3+} was also shown to bind to cysteine residues in reduced forms of those proteins without correct folding, thereby inhibiting spontaneous oxidative protein folding (i.e., through disulfide bond formation) and suppressing chaperone-mediated disaggregation/refolding of proteins *in vitro*.[41,48,49] Additionally, this inhibition of oxidative refolding can be aggravated by iAs^{3+}-induced depletion of intracellular reduced glutathione, which binds to iAs^{3+} and suppresses its interaction with cysteine sulfhydryl groups in proteins.[48]

Arsenic exposure may also perturb the functions of molecular chaperones by inducing their aggregation.[41] For instance, Hsp104p in yeast cells was found to undergo aggregation and redistribution upon exposure to iAs^{3+}, which may exacerbate protein aggregation by disrupting cells' ability in dissolving misfolded protein aggregates in the presence of free iAs^{3+}.[41]

As noted above, arsenic exposure can disrupt mitochondrial homeostasis, which stimulates ROS production and attenuates intracellular ATP levels. Therefore, iAs^{3+} can inhibit the binding of substrates to chaperones and diminish ATP supply for ATP-dependent chaperones, as observed for the TRiC chaperonin complex in *Saccharomyces cerevisiae*.[42] Along this line, we reason that DnaJ, which harbors two Cys_4-type zinc fingers,[50] may also be inhibited by iAs^{3+} binding and ROS, thereby impairing its recognition of denatured protein substrates and its regulation of HSP70.[51]

3.3. Induction of Pro-inflammatory Pathways and ER Stress.

Inflammation is an immune response triggered by pathogen infection or tissue injury; chronic inflammatory response not only activates innate and adaptive immune cells but also releases ROS.[52] A wide range of cellular, animal, and epidemiological studies showed that exposure to iAs^{3+} can activate pro-inflammatory signaling pathways, which aggravate oxidative stress and compromise proteome integrity.[53–57] Acute (i.e., 24 h) and chronic (i.e., 90 days) exposure of laboratory animals to iAs^{3+} induces pro-inflammatory modulators while reducing the expression of phagocytic receptors on immune cells (e.g., monocytes and granulocytes) and $CD4^+$ T cell subpopulation in serum, lung, brain, spleen, and thymus.[56–58] Likewise, cellular and epidemiological studies revealed that exposure to low doses of iAs^{3+} and MMA^{III} can lead to persistent inflammation.[53,54,59,60] Moreover, Fry et al.[55] observed that prenatal arsenic exposure results in NF-κB activation in infants (Table 1).

Molecular mechanisms have been proposed to account for the arsenic-elicited inflammatory response. This inflammatory effect is believed to originate from iAs^{3+}- or MMA^{III}-induced oxidative stress, which up-regulates ERK1/2, JNK, p38, and their downstream transcription factors including NF-κB, AP-1, and Nrf2.[56,60] Prolonged inflammation also initiates ER stress and unfolded protein response (UPR), where iAs^{3+}-induced up-regulations of GRP78, IRE1, ATF4, and ATF6α exacerbate protein misfolding and aggregation.[61–65]

Last but not least, several cellular studies reveal that exposure to iAs^{3+} or DMA^V significantly augments the expression of *APP* gene, which is accompanied by diminished expression of peroxisome proliferator-activated receptor-γ (PPARγ), a negative regulator of BACE-1 (β-secretase).[66–68] Furthermore, iAs^{3+}-elicited oxidative stress induces a prooxidant and inflammatory environment, which facilitates APP processing and increases Aβ oligomerization, thereby exacerbating amyloidogenesis and pathogenesis of Alzheimer's disease (Table 1).[68]

3.4. Impairment of Protein Clearance and Degradation Machineries.

Exposure to iAs^{3+} in drinking water also impairs the protein clearance and degradative machineries in the proteostasis network through disrupting the ubiquitinproteasome system

(UPS), autophagy, as well as asymmetric segregation and axonal transport of damaged proteins (Table 1).

3.4.1. UPS.—UPS is the major cytoplasmic machinery responsible for the degradation of the majority of short-lived, damaged, or misfolded proteins in eukaryotic cells.[69] UPS consists of complex ubiquitination cascades mediated by a concerted network consisting of E1, E2, and E3 enzymes, ubiquitin-modifying enzymes (e.g., deubiquitinating enzymes, SUMO-dependent ubiquitin ligases), and the 26S proteasome.[69] In this pathway, misfolded proteins destined for turnover are conjugated with ubiquitin, especially with the K48-linked polyubiquitin chains, recognized by p97 (i.e., an AAA+ ATPase) in complex with ubiquitin adaptors, and degraded by the 20S proteasome.[70,71]

Arsenic species were shown to perturb the efficient turnover of misfolded and aggregated proteins through disrupting the functions of the UPS.[72] This may proceed through (i) impairing the enzymatic activities of zinc finger (ZnF)-containing E3 ubiquitin ligases[73–75] and (ii) compromising the functions of p97 and proteasome (Table 1).[72]

iAs^{3+} can bind directly and selectively to Cys_4- and Cys_3His_1-type ZnF motifs, and this binding displaces their bound Zn^{2+} ions.[76] In addition, iAs^{3+} interacts directly with a number of RING finger (i.e., a specific type of ZnF) proteins, some of which are involved in protein ubiquitination.[73–75,77] In this vein, an acute 24-h exposure to arsenite diminishes, in a dose-dependent manner, the enzymatic activities of RNF20-RNF40, Rbx1, and FANCL RING finger E3 ubiquitin ligases, as manifested by the decreased ubiquitinations of their substrate proteins.[73–75] This raises the possibility that exposure to iAs^{3+} may inhibit other ZnF-containing regulatory proteins in the UPS, especially RING finger E3 ubiquitin ligases.[78]

Arsenate exposure also perturbs the functions of p97 and proteasome.[72] The ATP-dependent segregase activity of p97 is critical for extracting ubiquitinated, misfolded proteins for ATP-driven protein unfolding prior to proteasomal degradation.[71] The optimal functions of p97 and proteasome, which depend on a well-timed ATPase cycle, are crucial for the maintenance of cellular proteostasis,[71] as manifested by the observations of impairment of p97 in neurodegenerative diseases.[79,80] Interestingly, arsenate enhances the ATPase activities of p97, which augments ATP hydrolysis rate and diminishes the activity of p97.[72] Moreover, iAs^{3+} exposure leads to depletion of cellular ATP pool (*vide supra*),[43] which may disrupt cells' ability to empower the ATP-dependent clearance of misfolded proteins via the UPS.

3.4.2. Autophagy.—Autophagy is an evolutionarily conserved process in eukaryotes, where long-lived proteins, macro-molecular assemblies, and dysfunctional organelles (e.g., mitochondria) are eliminated through segregation into autophagosomes and subsequent degradation in lysosomes.[81] Autophagy, as another critical degradative machinery of the proteostasis network,[82] is often activated to enhance protein turnover under stress conditions, and loss of autophagy can contribute to neurological diseases.[83]

Growing lines of evidence indicate that arsenic exposure can disrupt autophagy,[84–87] and this occurs through (i) impairment of TORC1-mediated protein sequestration into autophagosome,[85,88] (ii) inhibition of autophagic flux via sustained Nrf2 activation,[84,89] and (iii) suppression of autophagosome-lysosome fusion (Table 1).[86,87]

TORC1 is a protein kinase known for its regulatory role in eliminating insoluble protein aggregates through sequestration into autophagic vesicles (a.k.a. autophagosomes) in cells.[88,90] Interestingly, acute exposure of *S. cerevisiae* to high concentrations of iAs^{3+} (50–200 μM, 10 min) and chronic exposure of BEAS-2B cells to a low dose of iAs^{3+} (250 nM, 16 weeks) both lead to TORC1 inhibition.[85,88]

iAs^{3+} has also been proposed to inhibit autophagic flux, which perturbs proteostasis through inefficient elimination of protein aggregates.[84] Acute exposure to low doses of iAs^{3+} (125–500 nM, 4 h) was shown to dysregulate autophagic influx in various human cell lines through prolonged activation of Nrf2, and this process depends on p62, but independent of Cys151 in Keap1.[84] Interestingly, Nrf2 protein can also be activated upon a 24-h exposure to 5 μM iAs^{3+}, which involves the direct binding of As^{3+} to the RING finger domain of Rbx1 and the ensuing inhibition of the activity of the Keap1-Cul3-Rbx1 E3 ubiquitin ligase complex.[74] This gives rise to diminished ubiquitination and turnover of its substrate protein(i.e., Nrf2).[74]

Low concentration of iAs^{3+} inhibits the fusion between autophagosome and lysosome,[87] which involves three SNARE proteins (STX17, SNAP29, and VAMP8).[91] *O*-GlcNAcylation of SNAP29 suppresses autophagosome-lysosome fusion and results in aberrant autophagic flux by suppressing the formation of the active SNARE complex (STX17-SNAP29-VAMP8).[91] In addition, Dodson et al.[87] demonstrated that acute iAs^{3+} exposure (0.5–2 μM, 4 h) augments the *O*GlcNAcylation of SNAP29, which subsequently perturbs the formation of the SNARE complex and suppresses autophagic flux. Lastly, iAs^{3+}-induced inhibition of autophagy also proceeds through sustained overproduction of IL-6, which enhances the interaction between Mcl-1 and Beclin-1 through STAT3.[85]

3.4.3. Asymmetric Segregation and Axonal Transport of Damaged Proteins.

—Under normal circumstances, the above mentioned cellular PQC systems have adequate capacity to dispose and eliminate misfolded or damaged proteins. However, once the amount of misfolded proteins exceeds the degradative capacity of the proteostasis network in higher eukaryotes, these misfolded proteins can aggregate and be partitioned into aggresomes at the microtubule-organizing center (MTOC) in the forms of juxta nuclear quality control compartment (JUNQ) and insoluble protein deposit (IPOD).[92,93] Interestingly, during cytokinesis, damaged (e.g., carbonyl modified) and aggregated proteins in aggresomes are asymmetrically segregated to mother cells, whereas daughter cells are devoid of these aberrant proteins through a polarisome- and tropomyosin-dependent polarized flow of misfolded proteins.[94,95] Therefore, this spatial PQC confers cellular fitness and prevents clonal senescence at the expense of mother cells under stress conditions.[96,97]

Proper asymmetric segregation of protein aggregates during cell division largely depends on the correct orientation and position of the mitotic spindle.[98] iAs^{3+} is well documented to

disturb mitotic progression.[99–101] Specifically, exposure to iAs^{3+} attenuates microtubule dynamics and induces abnormal mitotic morphologies including augmented polar distance and abnormal patterns of assembly/disassembly of mitotic spindles in exposed cells.[102] Additionally, acute exposure to low levels of iAs^{3+} disrupts the positioning of mitotic spindles through the PIP4KIIγ/Rho pathways (Table 1).[99]

Asymmetric axonal transport of misfolded and damaged proteins is also critical to proteostasis in neurons, as reflected by aberrant accumulation of damaged organelles and proteins in human neurodegenerative diseases manifesting axonal pathologies.[103] Axonal integrity is maintained by neurofilaments, microtubules, and actin filaments, which were shown to be impaired upon iAs^{3+} exposure.[104,105] As noted above, the eukaryotic chaperonin TRiC can be inhibited by iAs^{3+}, and this inhibition perturbs the folding and subsequent oligomerization of cytoskeleton components (e.g., α/β-tubulin and actin) into microtubules and actin filaments.[42] A single exposure of rodents to iAs^{3+} via intravenous injection leads to a time- and dose-dependent diminution in light subunit of neurofilaments, which compromises axonal transport.[104,105] Therefore, iAs^{3+}-elicited disruption of cytoskeletal protein components in axons impairs protein clearance by perturbing asymmetric axonal transport.

Hyperphosphorylated tau may also influence axonal transport.[106] iAs^{3+} exposure significantly increases the phosphorylation levels of several amino acid residues in tau (i.e., Thr-181, Ser-202, Thr-205, Thr-231, Ser-262, Ser-356, Ser-396, and Ser-404).[107] The hyperphosphorylated tau can trigger microtubule depolymerization, owing to its diminished affinity toward microtubules and augmented formation of amorphous tangles;[108] this may increase the likelihood of developing Alzheimer's disease upon arsenic exposure.[109]

Taken together, iAs^{3+} exposure compromises cytoskeleton functions in cells, which affect asymmetric axonal transport and partitioning of protein aggregates during cell division, thereby impairing the clearance of damaged proteins (Table 1).

4. CONCLUSIONS AND PERSPECTIVES

In this review, we surveyed recent epidemiological and laboratory-based studies on the effects of arsenic exposure on compromised protein quality control and discussed various pathways through which iAs exposure perturbs the proteostasis network and leads to pathogenesis of human diseases associated with protein misfolding. The physiological regulation of the proteostasis network involves a complex interplay of multiple pathways. [10,11,40] Exposure to environmentally relevant levels of iAs^{3+} targets multiple elements of the proteostasis network, encompassing mitochondria, chaperone network, immune systems, ubiquitin-proteasome system, autophagosome, and cytoskeleton. Hence, chronic arsenic exposure can result in a progressive decline in the capacity of refolding and clearance of misfolded/aggregated proteins, and the robustness of stress response pathways (Figures 2 and 3), thereby resulting in protein-misfolding diseases.

Apart from excessive ROS production, the findings cited in this review also suggest that the binding of iAs^{3+} with ZnF proteins, especially those RING finger E3 ubiquitin ligases

involved in protein ubiquitination,[73–75,77] constitutes one of the molecular mechanisms underlying arsenic-induced loss of proteostasis. In addition, exposure to iAs^{3+} induces ROS and reactive nitrogen species (RNS), including NO, may result in inadvertent *S*-nitrosylation of redox-sensitive cysteine thiolates in critical proteins, for example, poly(ADP-ribose) polymerase 1.[110] Thus, arsenite-elicited ROS/RNS, in conjunction with direct iAs^{3+} binding to sulfhydryl groups of critical cysteines in proteins, may also represent an important mechanism for the exacerbated proteostasis capacity in arsenic-elicited protein-misfolding diseases (Figure 4).

Although a lot has been learned about the arsenic-elicited disruption of the proteostasis network, much remains to be done to further explore their implications in public health and to illustrate the underlying molecular mechanisms. First, a majority of the previously published studies were conducted by employing moderate to high concentrations of arsenic species (i.e., over 5 μM in 24 h) in cell-based systems. It will be important to examine whether the findings from these previous studies can be extended to exposure conditions using lower concentrations of arsenic species that are more commonly encountered during environmental exposure or cancer therapy.[111] In this vein, it will be vital to differentiate the perturbations of the proteostasis network arising from the cytotoxic effects of high-dose exposure from those emanating from physiologically relevant doses of arsenic exposure. Moreover, inorganic arsenic species are known to undergo metabolic transformations to yield organic arsenic species in cells and tissues, as discussed above.[15] Hence, some of observed proteotoxic effects revealed from cellular and animal studies with the use of inorganic arsenic species may arise, in part, from their methylated metabolites.

Second, ribosome-associated protein quality control (RQC) pathway was recently found to be initiated and modulated by regulatory ubiquitinations mediated through several E3 ubiquitin ligases, which enable quality control of translational infidelity at ribosomes.[112–115] RQC is an evolutionarily conserved and energetically beneficial pathway for cells to predict, detect, and remove any potential errors at the earliest time points and locations from which potentially erroneous nascent polypeptides originate.[116] On the basis of the well-documented interactions between As^{3+} and ZnF proteins, it will be important to examine if iAs can also perturb RQC by binding to and impairing important E3 ubiquitin ligases in this pathway (e.g., ZNF598 and listerin).[116] Along this line, a recent study showed that iAs^{3+} binds to ZNF598 and perturbs its regulatory ubiquitinations of ribosomal proteins RPS10 and RPS20, thereby promoting ribosomal read-through of the stalling poly(adenosine) sequence in the coding region.[117]

Third, prolonged exposure to arsenite was shown to accelerate the natural processes of aging, as manifested by significant decrease of lifespan in *C. elegans* mediated by the DAF-16/FOXO transcription factor.[47] The close interconnection between FOXO transcription factors and sirtuin proteins,[118] along with the known disruption of sirtuin 1 and DAF-16/FOXO by chronic low-dose iAs^{3+} exposure,[47,119] suggests a mechanistic basis for the iAs^{3+}-induced disruption of proteostasis through the common pathways associated with longevity and stress response.

Lastly, many ZnF proteins are critical regulators of protein PTMs, especially ubiquitination, SUMOylation, and PARylation;[120] thus, it will be important to systematically investigate how exposure to iAs^{3+} modulates these PTMs at the entire proteome level. It will also be important to examine how arsenic exposure perturbs proteostasis by compromising the cross-talk among ubiquitination, SUMOylation, and PARylation of proteins.[121] For instance, SUMOylation can modulate proteostasis by not only altering a protein's solubility but also cooperating with, complementing, and balancing the ubiquitinproteasome system.[121] These studies will offer comprehensive insights into how As^{3+} exposure compromises the proteostasis network by modulating PTMs of cellular proteins.

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Biographies

Lok Ming Tam earned his B.S. degree in Cell and Molecular Biology from Chinese University of Hong Kong (Hong Kong SAR) in 2014 and studied Environmental Toxicology at the University of California Davis for 1 year. He subsequently joined the graduate program in Environmental Toxicology at the University of California Riverside. He worked under the guidance of Prof. Yinsheng Wang and received his Ph.D. degree in late 2019. His research interests include protein quality control and etiology of human diseases, with a special focus on the arsenic impairment of proteostasis.

Yinsheng Wang is currently a Distinguished Professor in the Chemistry Department and the Environmental Toxicology graduate program at the University of California Riverside. His research interest includes DNA damage and mutagenesis, proteomics, and epigenetics. In recent years, he also developed a strong interest in understanding the molecular mechanisms through which arsenic exposure elicits toxicity and carcinogenicity. His co-workers employ an multidisciplinary approach, encompassing mass spectrometry-based bioanalytical chemistry, organic chemistry, molecular biology, genetics, and genomics, to tackle their research projects.

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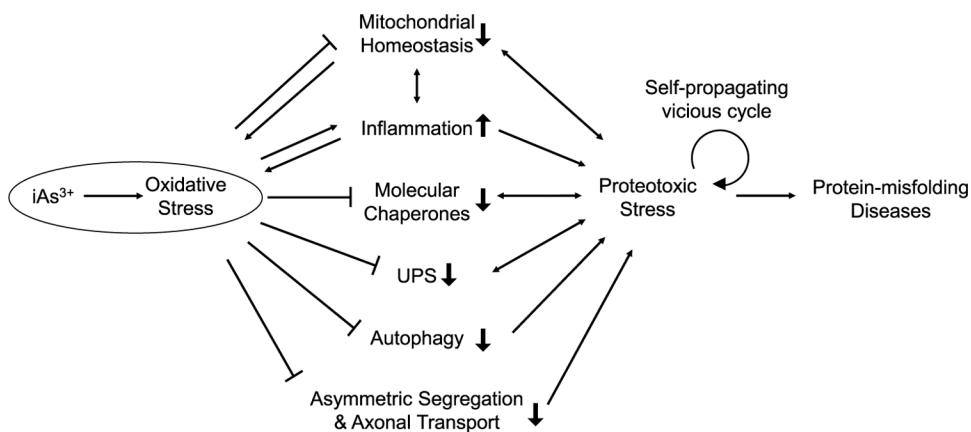
Figure 1.
Schematic diagram illustrating the molecular mechanisms through which iAs^{3+}-elicited oxidative stress induces proteotoxicity via targeting various elements of the proteostasis network, resulting in protein-misfolding diseases. Double-headed arrows denote the mutual interaction between the designated components of the proteostasis network and proteotoxic stress.
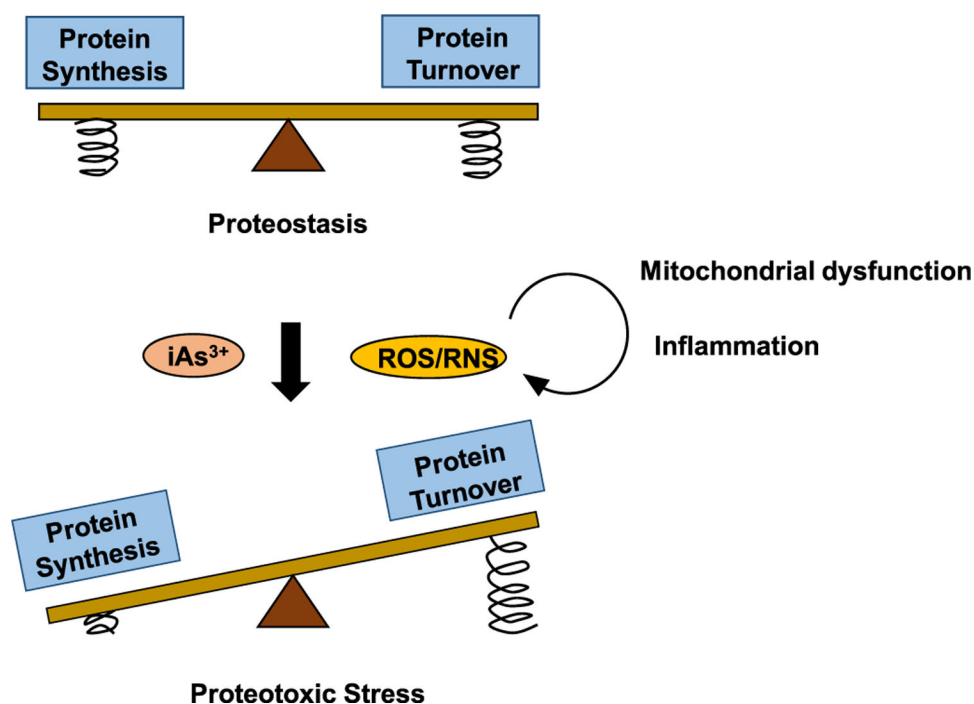
Figure 2.
Proteostasis is achieved by sustaining a balance between protein synthesis and protein turnover, with arsenic exposure and arsenic-elicited overproduction of ROS/RNS tipping the equilibrium away through impairing the degradative capacity of the proteostasis network. Arsenic exposure diminishes the folding capacity of molecular chaperones, resulting in the increased formation of misfolded/aggregated proteins. In addition, arsenic exposure and ROS/RNS impair the UPS, autophagy, and asymmetric segregation and axonal transport of damaged proteins, reducing the degradative capacity of the proteostasis network. Mitochondrial dysfunction and inflammation induced by arsenic exposure form a vicious self-feeding cycle of excessive ROS/RNS production, further aggravating proteotoxic stress through the imbalance between protein synthesis and turnover. Compression spring in the image represents the feedback mechanisms regulating the PQC machineries of protein synthesis or those of protein turnover. Arsenic and ROS/RNS can perturb the feedback signaling pathways involved in the PQC.
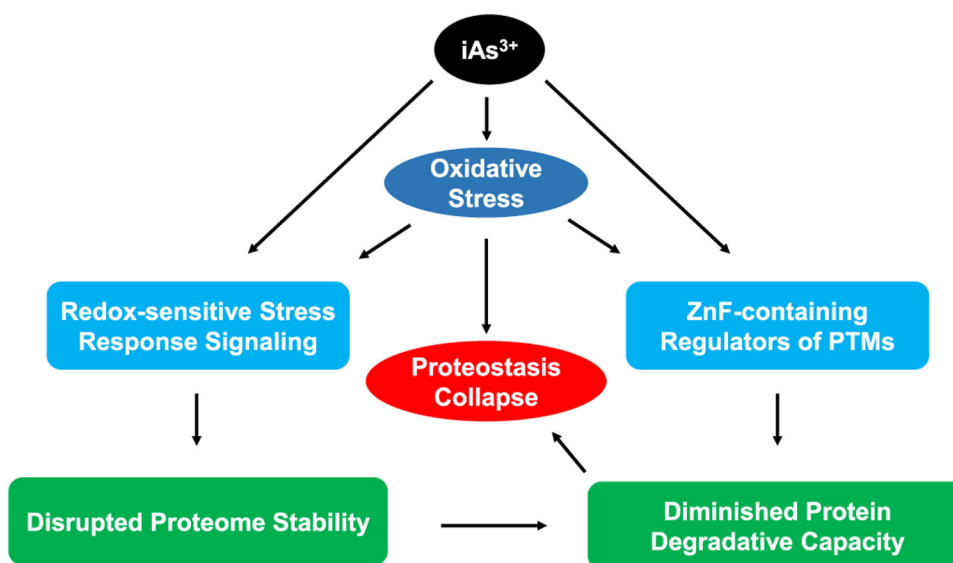
Figure 3.
iAs^{3+} and iAs-induced oxidative stress elicit proteostasis collapse through disrupting the functions of ZnF proteins and redox-sensitive stress response signaling pathways. iAs-elicited oxidative stress and iAs^{3+} itself can disrupt post-translational modifications (e.g., ubiquitination, SUMOylation, and PARylation), which are mediated by ZnF-containing enzymes and critical for robust degradative capacity of the proteostasis network. Meanwhile, iAs^{3+} and ROS/RNS can impair redox-active stress response signaling (e.g., oxidative stress response, heavy metal response), which prolong cellular functions at the expense of disrupted proteome stability. Combined together, the diminished protein degradative capacity of the proteostasis network leads to proteotoxicity, ultimately resulting in protein-misfolding diseases.
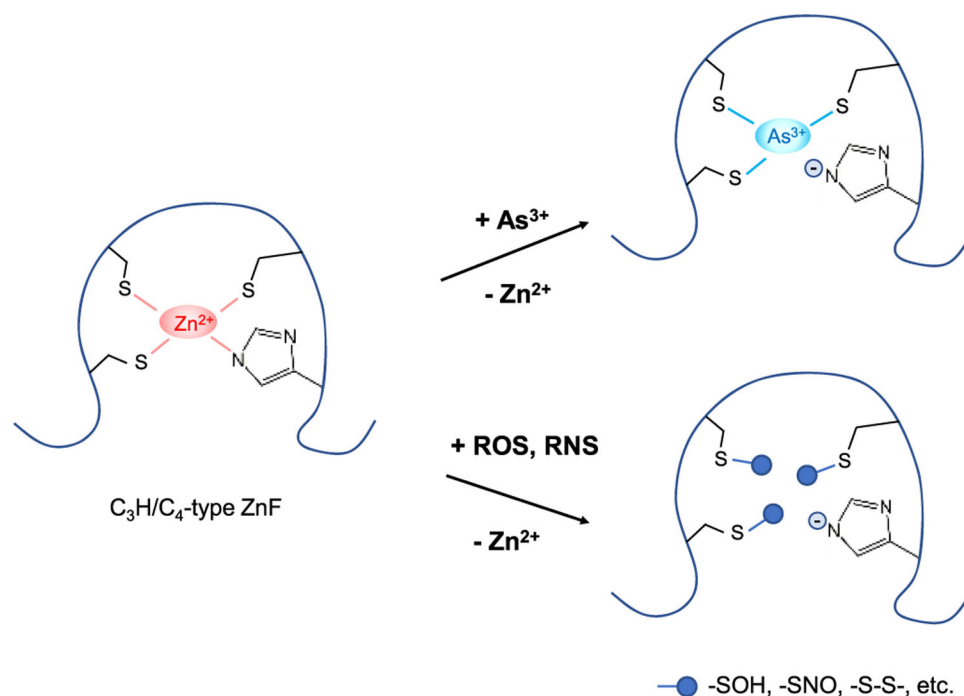
Figure 4.
Modes of action of iAs^{3+} and iAs-elicited ROS/RNS in compromising the enzymatic activities of ZnF proteins. iAs^{3+} and ROS/RNS can target vicinal cysteines within the zinc coordination spheres of these proteins: (i) iAs^{3+} binds directly to these cysteines more tightly than Zn^{2+}; (ii) ROS modify these cysteines to yield a series of oxidation products, such as −SOH and −S−S−; (iii) RNS, especially NO and peroxynitrite, can *S*-nitrosylate these cysteines. In all these cases, Zn^{2+} ions are released from the ZnF domains, which alter the conformations of ZnF proteins and perturbs their enzymatic activities.

Table 1.

Summary of Key Findings Associated with Arsenic-Induced Compromised Protein Quality Control

components of the proteostasis network	experimental system	Reagent used	concentration; exposure time	refs
Mitochondrial Homeostasis				
mitochondrial DNA damage	A$_L$ human-hamster hybrid cells, CHOK1 cells stably expressing a single copy of human chromosome 11	NaAsO$_2$	0.5–1 μg/mL; 60 d	26
uncoupling of mitochondrial respiration through metabolic reprogramming	C. elegans	NaAsO$_2$	50, 250, or 500 μM; 12–48 h	27
	Cultured human cells (BEAS-2B, RWPE-1, A549, HUC and HDF)	NaAsO$_2$	0, 1, or 5 μM; 1–2 wk	30
	BEAS-2B, cancer stem-like cells	NaAsO$_2$	0.25 μM; 3–7 d	31
excessive production of ROS	A$_L$ hybrid cells	NaAsO$_2$	2 μg/mL; 5 min	25
	3xTgAD mouse model	NaAsO$_2$	3 ppm (0.2 mg/kg/day); 6 mo	28
elevated proton leak by ROS-induced depolarization and lipid peroxidation	C. elegans	NaAsO$_2$	0, 50, or 500 μM; 48 h	27
Molecular Chaperones				
interference with substrate binding to chaperone proteins	S. cerevisiae	NaAsO$_2$	1 mM; 1 h	42
disruption of activities of ATP-dependent chaperones	HeLa cells	NaAsO$_2$	50, 100, 200, 400, 500 μM; 1–4 h	43
induction of protein aggregation of molecular chaperones	S. cerevisiae	NaAsO$_2$	50, 100, 200, 400, 600 μM; 120 min	41
	1-day-old male chickens/cocks	As$_2$O$_3$	7.5, 15, and 30 mg/kg	45
	In vitro (e.g., murine NIH-3T3 cells) and in vivo (e.g., rodent)	NaAsO$_2$	1–300 uM; 1–16 h (in vitro); 0.8–6 mg/kg; 1–24 h (in vivo)	44
	GM00637 human fibroblast cells	NaAsO$_2$	5 μM; 24 h	46
	C. elegans	NaAsO$_2$	100 mM; 4 d	47
Pro-inflammatory Pathways and ER Stress				
activation of inflammatory response	porcine cells from fresh aortas	NaAsO$_2$	0.5, 2, 5 μM; 0.5–2 h	53
	circulating lymphocytes from arsenic-exposed human subjects	Blood arsenic	0–4.32, 4.64–9.00, 9.60–46.50 μg/L	54
	human infants born to arsenic-exposed mothers	Arsenic	maternal toenail 0.5 μg/g	55
	female C57BL/6 mice (6–7 weeks old)	NaAsO$_2$	0, 2.5, 5, 10 mg/kg; 24 h	56
	male Sprague-Dawley rats	NaAsO$_2$	0, 5, 10, 20, 50, 100 ppb; 7, 14, or 28 d	57

components of the proteostasis network	experimental system	Reagent used	concentration; exposure time	refs
reduction of phagocytic receptors on immune cells	exposed rural women from districts of 24 Parganas (south)	arsenic	11–50 μg/L; lifetime (22–45 yr)	58
induction of ER stress	RIN-m5F rat insulinoma pancreatic β-cell line	As_2O_3	0, 2, 5 μM; 8, 16, 24 h	61
	SKH-1 hairless mice	$NaAsO_2$	50, 100, 200 ppm; 1 mo	62
	RAW 264.7 mouse macrophage cells	As_2O_3	0, 0.2, 2 μM; 1 or 3 h	63
	Neuro-2a murine neuroblastoma cells	As_2O_3	5 μM; 6, 12, or 24 h	64
	SVEC4–10 mouse vascular endothelium cells	As_2O_3	5 or 7.4 μM; 16 h	65
enhanced APP processing and Aβ oligomerization	cholinergic SN56.B5.G4 cells, primary neuronal cells derived from transgenic Tg2576 mice overexpressing human APPswe	$NaAsO_2$ or DMA	5 or 10 μM; 12 or 24 h	66
	male Wistar rats	$NaAsO_2$	3.80 ppm; 68 d	67
Ubiquitin-Proteasome System				
impairment of enzymatic activities of ZnF-containing E3 ubiquitin ligases	GM00637, HeLa cells	$NaAsO_2$	1, 2, 4, 5 μM; 24 h	73
	HEK293T cells	$NaAsO_2$	1, 3, 5 μM; 24 h	74
	GM00637, IMR90, and HEK293T cells	$NaAsO_2$	5 or 20 μM; 8 or 24 h	75
	NB4 APL cells	As_2O_3	1–2 μM; 1–24 h	77
compromising functions of p97 and proteasome	NIH3T3, DTC25 cells	arsenate	50 or 250 μM; 0–25 min or 16 h	72
Autophagy				
impairment of TORC1-mediated protein sequestration to autophagosome	BEAS-2B cells	$NaAsO_2$	0.25 μM; 24 h, 1 wk or 16 wk	85
	S. cerevisiae	$NaAsO_2$	50, 100, 200, 500 μM; 5, 10, or 30 min	88
inhibition of autophagic flux via sustained Nrf2 activation	HEK293T cells	$NaAsO_2$	1, 3, 5 μM; 24 h	74
	BEAS-2B, HBE cells	$NaAsO_2$	125, 250, 500 nM, 1, 4, or 10 uM; 4 or 16 h	84
	HaCaT human keratinocytes	$NaAsO_2$	8 uM; 6 h	89
suppression of autophagosome-lysosome Fusion	NIH3T3 cells	$NaAsO_2$	0.25, 0.5, 1, or 2 μM; 2 or 4 h	86
	HeLa, HEK293T, NIH3T3, iBMKs cells	$NaAsO_2$	0, 0.5, 1, 2 μM; 4 h	87
sustained overproduction of IL-6	BEAS-2B cells	$NaAsO_2$	0.25 μM; 24 h, 1 wk or 16 wk	85
Asymmetric Segregation and Axonal Transport of Damaged Proteins				
disturbed mitotic progression and aberrant positioning of mitotic spindles	G$_2$-enriched HFW cells	$NaAsO_2$	5 μM; 18 h	99
	HeLa-S3, CGL2 cells	$NaAsO_2$	1 or 3 μM; 20 h	100

components of the proteostasis network	experimental system	Reagent used	concentration; exposure time	refs
attenuated microtubule dynamics and abnormal mitotic morphologies	HeLa-S3 cells	NaAsO₂	5, 10, 20, 50 μM; 1, 2, or 24 h	102
Asymmetric Segregation and Axonal Transport of Damaged Proteins				
inhibition of TRiC for folding and oligomerization of cytoskeleton components	*S. cerevisiae*	NaAsO₂	1 mM; 3 h	42
decreased light subunit of neurofilament	male Wistar rats	NaAsO₂	15 or 20 mg/kg; 3, 6, or 9 h	106
augmented phosphorylation of tau	Chinese hamster ovary (CHO) T40 cells	NaAsO₂	500 μM; 2 h	107