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Pleiotropic roles of late embryogenesis abundant proteins of *Deinococcus radiodurans* against oxidation and desiccation

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ABSTRACT

Deinococcus radiodurans, an important extremophile, possesses extraordinary stress tolerance ability against lethal and mutagenic effects of DNA-damaging agents, such as γ-rays, ultraviolet, oxidation, and desiccation. How global regulators of this bacterium function in response to oxidation and desiccation has been an intense topic as elucidating such mechanisms may help to facilitate some beneficial applications in agriculture or medicine. Particularly, a variety of functional proteins have been characterized for *D. radiodurans*' behaviors under abiotic stresses. Interestingly, a group of Late Embryogenesis Abundant proteins (LEAs) in *D. radiodurans* have been characterized both biochemically and physiologically, which are shown indispensable for stabilizing crucial metabolic enzymes in a chaperone-like manner and thereby maintaining the metal ion homeostasis under oxidation and desiccation. The rapid progress in understanding deinococcal LEA proteins has substantially extended their functions in both plants and animals. Herein, we discuss the latest studies of *radiodurans* LEA proteins ranging from the classification to structures to functions. Importantly, the harnessing of these proteins may have unlimited potential for biotechnology, engineering and disease treatments.

Contents

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1. Introduction

Reactive oxygen species (ROS) refer to a variety of biologically important oxygenic radicals, such as hydroxyl ($OH^{\cdot}$), superoxide ($O_2^{\cdot-}$), peroxyl ($RO_2^{\cdot}$), and oxidizing non radicals (e.g., hydrogen peroxide, H_2O_2). ROS are generated during endogenous metabolism and may be induced by an exceedingly large quantity of oxidative stressors, including ionizing radiation (IR), UV radiation, desiccation, H_2O_2 and mitomycin C (MMC) [1–3]. The excessive production of ROS is highly detrimental to organisms and may cause severe and irreversible damage to genomic DNA, critical enzymes and vital proteins [3]. In humans, ROS-induced oxidative modification of cellular macromolecules may be directly associated with many pathophysiological conditions, including degenerative neurological diseases, cancers, atherosclerosis and diabetes [4,5]. Hence, better understanding of the biological mechanisms of ROS formation and host homeostasis ability to rapidly remove the harmful ROS has been an important topic in scientific research, which may offer some potential applications in agriculture, engineering, and medicine. Remarkably, a unique vegetative bacterium, named *Deinococcus radiodurans*, was isolated from canned ground meat treated by γ-irradiated at 4,000 Gray (Gy), which is approximately 250 times higher than the death dose used to kill *Escherichia coli* [6–8]. This outstanding survival and growth robustness of *D. radiodurans* under such harsh environments, including gamma radiation, oxidation, and desiccation, which may produce high-level ROS, has garnered great attention to scientists from diverse fields [9–11]. Consequently, *D. radiodurans* has been considered an ideal model bacterium to study the stress resistance against environmental fluctuations [3].

Several decades of intensive studies have revealed that *D. radiodurans* has evolved with multiple survival strategies, including gene regulatory systems, DNA repair pathways and antioxidation mechanisms, to coordinate a timely response, DNA fragments recovery and ROS removal, and survive from the most severe ionization, UV radiation, oxidation and desiccation [12–15]. Therefore, the global regulators of *D. radiodurans*, such as IrrE and DrRRA, were extensively studied [16–19]. Furthermore, these global regulators can heterologously improve stress resistance of the transformants in different host organisms by enhancing the expression of endogenous functional genes under various harsh conditions [17,20]. Recently, functional genes, especially the chaperones and chaperone-like proteins, have attracted great attention since stresses can ubiquitously damage the global regulators without the protection of these constitutively-expressed proteins [21–26]. Thus, investigating the protective mechanisms of the above-mentioned functional proteins will substantially enrich our knowledge of *D. radiodurans* for its extreme tolerance to devastatingly damaging oxidation.

To date, increasing functional proteins of *D. radiodurans* have been discovered and extensively characterized. In particular, three late embryogenesis abundant proteins (LEAs, encoded by *dr1172*, *dr0105* and *dr1372*) were shown to be responsible for resilient resistance to oxidation and desiccation stresses, of which DR1172 and DR0105 were classified into LEA family group 3 proteins (G3LEA), and DR1372 to the group 5 LEA proteins based on their amino acids identity [21,22,27–29]. LEA proteins were intensely studied in plants and classified into seven distinct groups according to the variance of their motifs that are strongly induced under water-loss conditions, oxidation and desiccation [30–32]. Previous studies of LEA proteins are restricted to eukaryotes, especially plants, but less was known about their function and underlying mechanisms in bacteria and archaea, even both were genetically annotated with diverse LEAs [21,22,33].

We will discuss functional characterization of *D. radiodurans* LEA proteins for coping with oxidation and desiccation from the microbial aspect. Our discussion will focus on the classification of LEA proteins and their structural flexibility during dynamic oxidative responses. Recent biochemical studies showed that DR1172 acted in a chaperone-like manner to protect the crucial enzymes from damage due to oxidation and desiccation. Furthermore, we will discuss the potential function of the LEA proteins, such as the nuclease activity and metal ions binding activity. Improved understanding of LEA proteins might generate insight into the design of novel therapeutic strategies for diseases involving cell damage, tissue injury, degeneration, aging and cell death.

2. Characterization of LEA proteins in *D. radiodurans*

2.1. Classification of LEA proteins in D. radiodurans

LEAs were coined by Galau et al., according to the induction and accumulation in a high level during the maturation phase of cotton (*Gossypium hirsutum*) [34]. Although the terminology of LEA proteins was not well established, with many homologous LEA proteins genetically discovered and functionally characterized, LEA proteins have been classified into at least seven groups on the basis of the amino acids information, especially the distinctive sequence motifs [35–37]. Groups 1, 2, 3, 4, 6, and 7 are typical members of the LEAs family and bear conserved hydrophilic motifs, and thus usually called “hydrophilins”. However, group 5 LEA proteins possess the high hydrophobicity without significant signature motifs and are thus considered as atypical LEA proteins [30,38]. Henceforth, some well-studied group LEA 3 and 5 proteins from plant, bacteria, fungi and animal were summarized in Table 1.

Recently, the roles of LEA proteins in *D. radiodurans* were elaborated in a succession of papers[21,22,42], among which three genes encoding LEA family proteins (locus tag *DR_1172*, *DR_0105* and *DR_1372*) were annotated in the genome of *D. radiodurans* (Table 2). Thus, DR1172 is rich in hydrophilic amino acids residues, which were clustered to a typical Hydrophilic Domain (HD) with 8 conserved motifs. Each of these motifs contains 11 amino acids (aa), which was generally described as 11-mer (Fig. 1A). On this basis, the DR1172 motifs appear to conform the general pattern of group 3 LEA proteins (G3LEA) consisting of multiple copies of an 11-mer motif and was accordingly classified into G3LEA proteins [43,44]. Likewise, DR0105 was also classified into group 3 LEA proteins based on the protein sequence identity [28,42]. Critically, deletion of *dr0105* in *D. radiodurans* had null effect on the ionizing radiation resistance [45,46]. Similar to DR1172, DR0105 was predicted to have an HD domain that consists of 8 conserved motifs, and each motif contains 16 amino acids (16-mer), which is distinct from the typical 11-mer of G3LEA. Hence, DR0105 was regarded as an atypical G3LEA protein. Due to the limited functional characterization of DR0105, the analysis of its protein sequence and other traits has attracted a little attention. In contrast, DR1372 is abundant in hydrophobic residues classified to the group 5 LEA protein, and thereby classified into G5LEA protein (Fig. 1B). The general information of these three LEA proteins in *D. radiodurans* was summarized in
Table2.

2.2. Structural transformation of LEA proteins in D. radiodurans adapting to challenging environments

Like the hydrophilins, most of the LEA proteins exhibit the hydrophilic property, which ubiquitously exist as random-coiled proteins in natural conditions [47,48]. Although some of the LEA members were predicted in an ordered structure based on the sequence-dependent computational modelling, nearly all of the experimentally-verified hydrophilic LEA proteins were in a

Table 1
Information of reported LEA proteins originated from plants, bacteria, fungi and animals.

Accession No.in GenBank	Group	Kingdom	Species	Amino acids of full length (aa)	Core domain	Reference
AAF10747.1	LEA3	Bacteria	*Deinococcus radiodurans* R1	298	HD	[21]
SEI35173.1	LEA3	Fungi	*Yarrowia lipolytica*	748	HD	[21]
NP_001256171	LEA3	Animal	*Caenorhabditis elegans*	733	HD	[21]
AB841344	LEA3	Animal	*Polypedilum vanderplanki*	143	HD	[39]
BAB88877	LEA3	Plant	*Brassica napus*	226	HD	[21]
NP_001146945.1	LEA3	Plant	*Zea mays L.*	182	HD	[40]
AAF10950.1	LEA5	Bacteria	*Deinococcus radiodurans* R1	164	WHy	[22]
ACJ46652.1	LEA5	Plant	*Lotus japonicus*	94	WHy	[41]

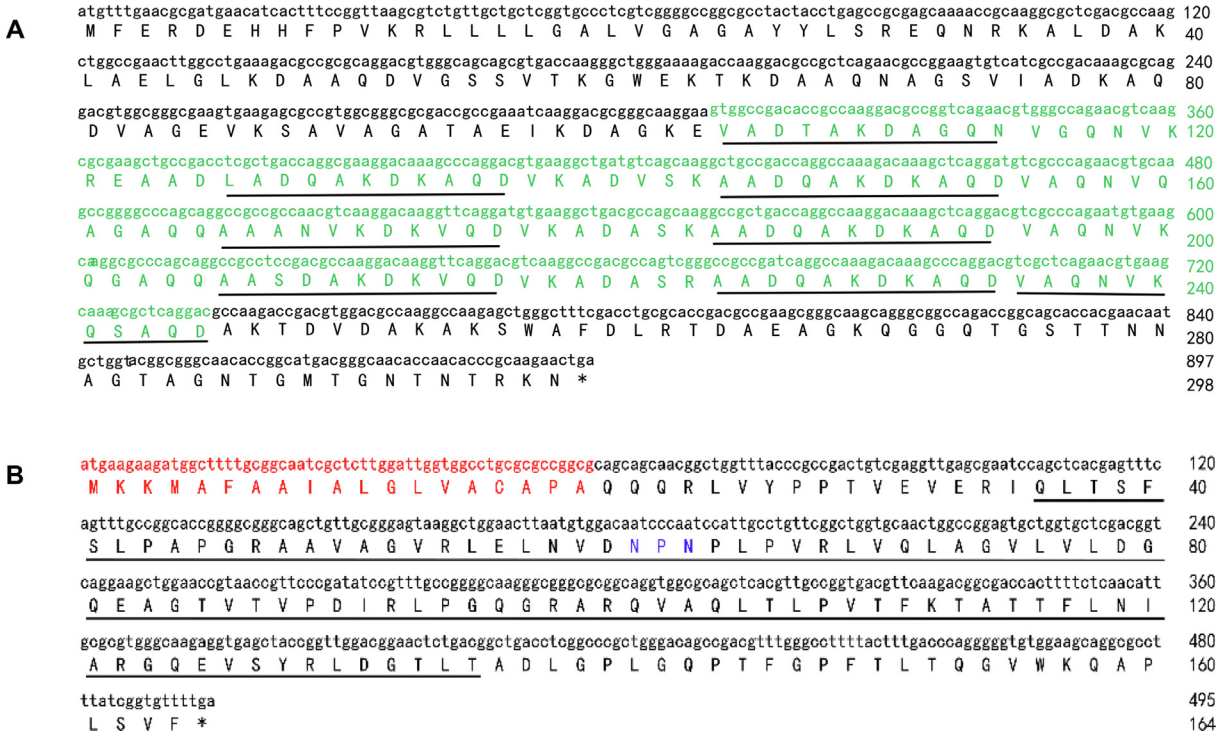

Fig. 1. Sequences of DR1172 and DR1372. A: The sequences of nucleic acids and amino acids of DR1172. The green letters indicate hydrophilic domain, and the underlines indicate the 8 motifs. B: The sequences of nucleotide acids and amino acids of DR1372. The N-terminal signal peptide is indicated in red letters. The WHy domain (Water stress and Hypersensitive response domain) is underlined. The NPN motif is indicated in blue letters. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Comparisons among group 3 and group 5 LEA proteins based on their amino acids (aa).

Accession No.in GenBank	Name	Amino acids of full length (aa)	Name of domain	Amino acids of domain (aa)	Molecular weight of domain (Da)	Grand average of hydropathicity (GRAVY)
AAF10747.1	DR1172	298	DrHD	142 (104–245)*	14,707	−1.034
AAF09701.1	DR0105	163	DrCD	103 (59–161) *	11,418	−0.1286
AAF10950.1	DR1372	164	DrwH	100 (36–136)*	10,586	0.128

Note: The asterisk indicates the position from the starting aa to the terminating aa. The hydrophilic domain (HD) of DrG3LEA (AAF10747.1) is named DrHD and contains 8 motifs. The positive value of grand average of hydropathicity represented the hydrophobicity, and in negative meant hydrophilicity. The grand average of hydropathicity of DrHD is −1.034. The core domain of DR0105 (GenBank: AAF09701.1) is named DrCD that contains 8 motifs. The core domain of DR1372 (AAF10950.1) is a WHy domain (Water stress and Hypersensitive response domain), and the grand average of hydropathicity is 0.128.

disordered conformation under standard physiological solutions [41,49–52]. Likewise, the hydrophilic LEA protein in *D. radiodurans*, DR1172, was not an exception. Our previous work focusing on HD of DR1172 demonstrated that HD was in a high relative abundance of random coils measured by circular dichroism (CD) up to 60 % under phosphate buffer indicating the intrinsically-unstructured conformation [21]. The presence of 50 % glycerol or 2, 2, 2-trifluoroethanol (TFE) mimicking the water-loss conditions (correspondent to the drought- and α-helix inducing-conditions, respectively) could instantaneously induce the disordered HD to form high-level α-helices [53,54]. Furthermore, recent structural characterization of the full-length of DR1172 revealed that the α-helix was maintained at around 45 % under an aqueous solution, and adding 10 mM Mn^{2+} or Zn^{2+} can respectively improve the abundance of α-helices [42]. In addition, eGFP-expressing DR1172 was observed primarily residing at the membrane, and membrane-tension mimicking strategy with 2 % SDS can significantly induce the degree of α-helix up to nearly 100 %, implying

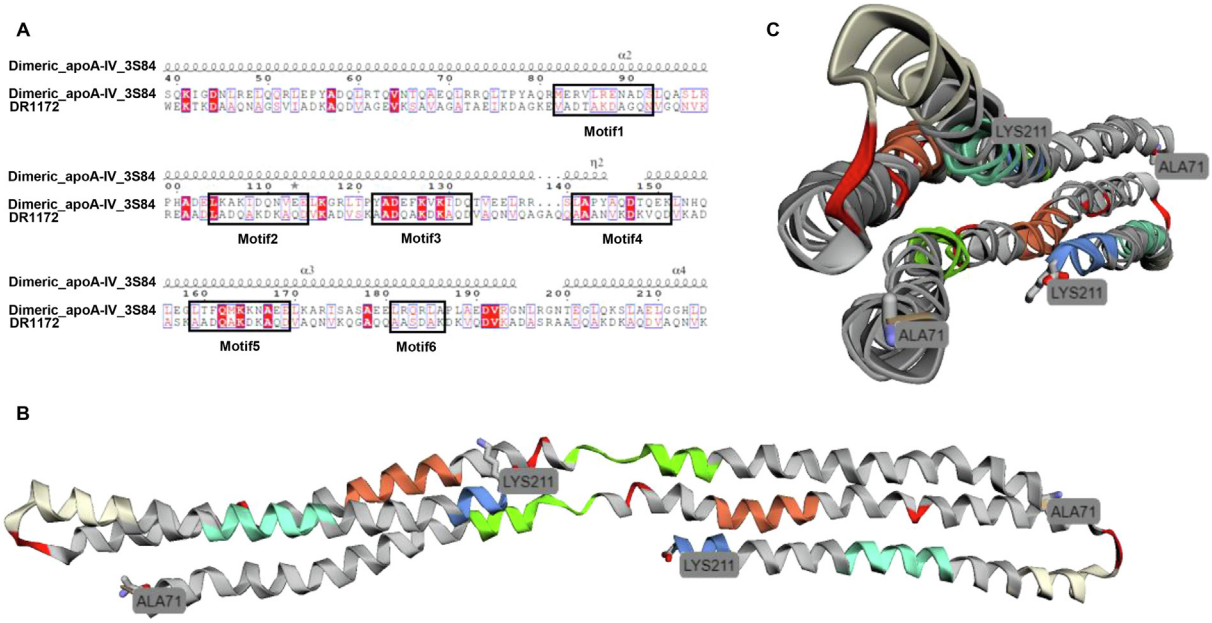

Fig. 2. Simulated structures of DR1172. A: Second structure prediction of DR1172. The sequences alignment was based on the NCBI Blast output referencing the Protein Data Bank (PDB). The boxes indicated the conserved motifs that were under the coverage with Dimeric apoA IV (PDB ID: 3S84). B, C: Three dimensional structure simulation of DR1172 that was in Dimeric arrangement. Five motifs were labelled orderly and visualized in the pallet colors of R: motif1 (chartreuse); motif2 (cyan); motif3 (coral); motif4 (cornsilk); motif5 (aquamarine); motif6 (cornflowerblue). The rest helices were shown in grey, and the red represented the non–alpha helix and beta sheet. Sticks showing the starting residue alanine (ALA71) and lysine as the ending residue (LYS211). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

that DR1172 may have the potential interaction with membrane-anchored molecules [42]. Of particular interest, the membrane-associated environment was identified with highly strict hydrophobicity [55,56], in which HD was likely soaked into cytosol with N- or C-terminal anchored in the membrane. Collectively, although the current studies unveiled the special structure of DR1172 and the core domains, the most important discovery was their structural transformation to adapt to fluctuated environments. Despite the recent discoveries, there is much more to be learnt, namely, screening for the crucial amino acids and resolving and elucidating three dimensional structures in greater detail and higher precision.

Unlike DR1172, DR1372 was classified in an atypical LEA group, LEA5C, containing a Water stress and Hypersensitive response (WHy) domain and signal peptides at N-terminal [22]. Bioinformatic analysis indicated that DR1372 is a novel hydrophobic protein based on the hydropathic index. The structural prediction suggested that DR1372 was in an orderly form and the structure was maintained by β strands, in which the WHy domain contained a conserved invariant triplet "NPN" motif [22]. Due to the protein's structural hindrance, relatively less interest was devoted to the structural analysis of DR1372, let alone exploring their structural characteristics under oxidative conditions. The hydrophobic property of DR1372 may hamper the protein acquirement via heterologous expression due to its low solubility. Thus, optimizing the expression of DR1372 seems to be prerequisite for further structural analysis.

To gain a better structural understanding of DR1172, a three dimensional structure was simulated by Swiss Model, in which the best hit was 3S84 (dimetric core domain of human apolipoprotein, apoA-IV) in Protein Data Bank and selected as the model template [57]. On this basis, almost 6 motifs (part of the motif 6) of DR1172 were covered and aligned (Fig. 2A). However, the remaining residues were computationally simulated to form the helices according to their hydrophilic property. According to the model template, DR1172 has the potential to form dimer within each monomer that is composed of 6 helical motifs (Fig. 2B and C). Considering the coverage limitation of the model template, collectively, we assumed that DR1172 constitutes of 8 helical motifs. In addition, the primary intrinsically-disordered structure of DR1172 can be instantaneously converted and condensed into high-level alpha helices in conditional stresses, and further likely to form polymer by self-association, such as the modelled dimeric arrangement [57,58]. We also speculated that DR1172 polymer-supported channels can provide larger protective cavity for the crucial proteins associated with DNA repair, cell respiration and metabolisms under a harsh condition.

Similarly, three dimensional structure of DR1372 was also modelled based on the LEA protein, 1YYC, from *Arabidopsis thaliana*. It is evident that DR1372 was composed of nine beta-sheets and two alpha-helices (Fig. 3A), which is in line with the characteristics of LEA group 5 [22,59]. The beta-strand barrel was formed as shown in Fig. 3B and C. Compared to the structural flexibility of DR1172, DR1372 appeared to primarily form the beta-sheet barrels, which was seemingly pre-prepared for crucial proteins in the case of stresses shifting. Whether the configurational changes of DR1372 barrels occur in a real world under abiotic stresses is still calling for further studies Fig. 4.

3. Function of LEA proteins: Mechanisms for stress-response

The function of proteins is generally defined by and/or largely dependent on their structure, thus the stress-induced structural flexibilities of LEA proteins were experimentally evaluated with diverse functions. In general, a typical characteristic of LEA proteins that acted as a similar role to "molecular shield" or chaperones [44,60–62]. LEA proteins can reduce the formation of protein aggregates when abiotic stresses occurred. For example, a group of LEA3 protein PvLEA4, from the sleeping chironomid *Polypedilum vanderplanki*, functions as a molecular shield by reducing the a-casein aggregation [39]. MtPM25, a member of the group 5 of *Medicago truncatula* was able to prevent the aggregation of

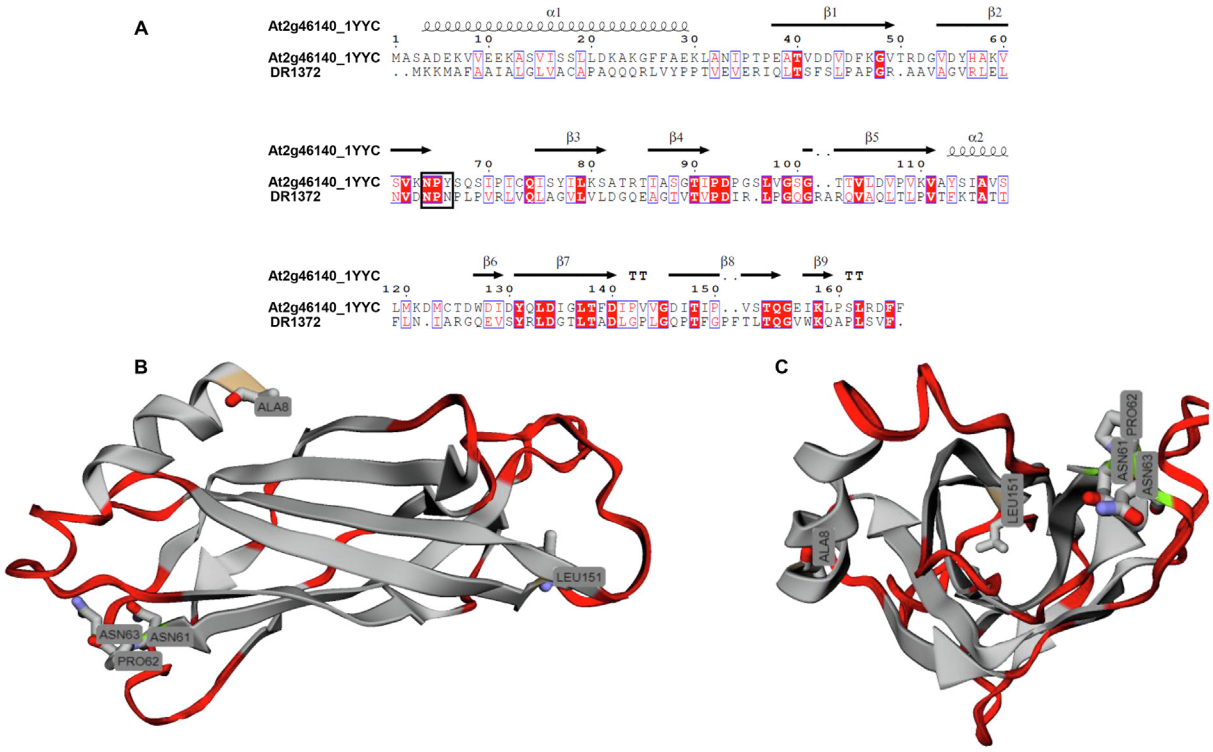

Fig. 3. Simulated structure of DR1372. A: Second structure prediction of DR1372. The best hit is 1YYC after NCBI blasting in PDB database. "NPN" was labelled in black box. B, C: Three dimensional structure of DR1372 simulated by Swiss Model. Sticks indicated the starting residue (ALA8), ending residue (LEU151), and the conserved "NPN" residues (ASN61, PRO62, and ASN63). The structures outside alpha-helix and beta-sheet were labelled in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

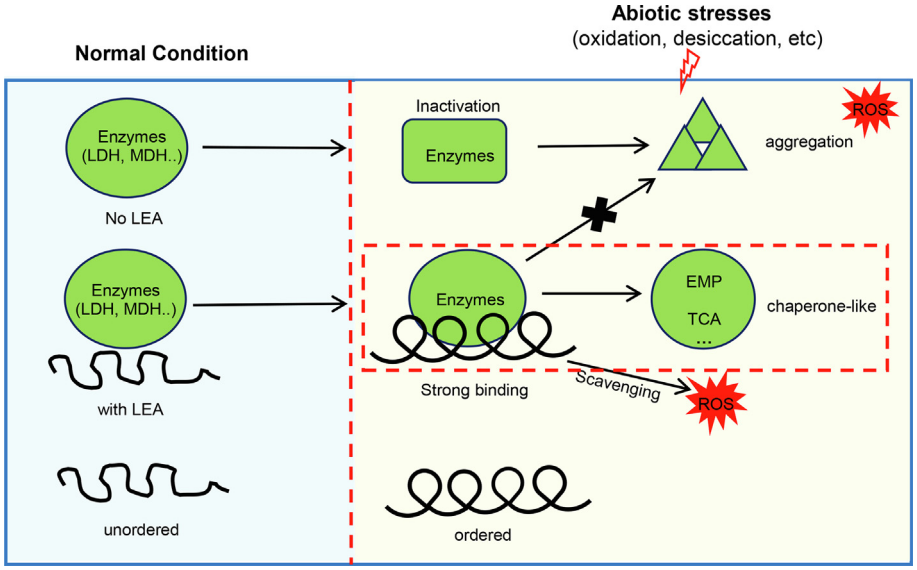

Fig. 4. Chaperone-like function model of LEA proteins. In the absence of a LEA, the enzymes undergo aggregation under stresses and thereby resulting in inactivation. In normal conditions, LEAs are disordered and can bind crucial enzymes in metabolic pathways, such as LDH or MDH, in a weak manner. Once stressed, LEAs become ordered and their interaction with the enzyme becomes stronger, preventing the enzyme from aggregation and maximally preserving its enzymatic activity. EMP: Embden-Meyerhof-Parnas pathway; TCA: tricarboxylic acid cycle.

water soluble proteome under desiccation and freezing stresses [63]. As previous studies described, a number of LEA proteins could protect crucial metabolic enzymes, such as lactate dehydrogenase (LDH), malate dehydrogenase (MDH), citrate synthase, fumarase, and rhodanese from freezing and desiccation damage to ensure cellular enzymatic function [64–66]. As most of the above researches were intensively investigated in plants and animals, they provided fundamental framework of studying LEA proteins. In addition, a recent report unveiled that LEA proteins in extremophilic *D. radiodurans* not only significantly improved stresses tolerance, but also displayed other novel functions, such as anchoring in membrane and binding to metal ions [42]. Therefore, the recent advances in understanding of the function of *Deinococcal* LEA proteins are noteworthy, which will be described below in detail.

3.1. Leas are involved in diverse abiotic stresses

With the progress in the framework studies, functional assessment and verification of LEA proteins in *D. radiodurans* were simultaneously carried out by phenotypic assays. The deletion of *dr_1172*, encoding typical group 3 LEA protein, sensitized *D. radiodurans* to desiccation and oxidation stresses [29,39]. Moreover, *in vivo* enzymatic activities, such as catalase (CAT) and superoxide dismutase (SOD) that are important components of antioxidant enzymes, were also downregulated in *dr_1172* mutant strain compared to the wild-type strain in the presence of H_2O_2. Recently, Dai et al., found that the absence of *dr_1172* led to an imbalance of intercellular Mn/Fe concentration ratio that was likely to crush the *in vivo* metal ion homeostasis and may be considered as one of the antioxidant defense systems [42]. Likewise, the inactivation of *dr_1372*, encoding DR1372 classified into a typical group 5 LEA protein, similarly caused an increased sensitivity to oxidative stress, in which the measured antioxidant enzymatic activities were impaired in comparison to the wild-type counterpart [22]. Taken together, both LEA proteins DR1172 and DR1372 may be indispensable for oxidation resistance of *D. radiodurans*.

3.2. LEA proteins confer abiotic resistance to E. Coli

An alternative approach for functional studies of LEA proteins is heterogeneous gene expression. There are numerous studies by introducing LEA proteins into plants and microbes, in which stress tolerance was evidently enhanced [67–72]. Our recent work discovered that *E. coli* expressing the recombinant HD of group LEA 3 proteins derived from four different organisms were more tolerant to desiccation and H_2O_2 than the control *E. coli* without recombinant HD [21]. Importantly, the DrHD, a hydrophilic domain of DR1172 in *D. radiodurans*, displayed the strongest viability under oxidation stress compared to other strains [21]. Consistent with our findings, Jiang et al., also characterized the WHy domain of group LEA5, a hydrophobic domain of DR1372 from *D. radiodurans* using a similar approach, demonstrating that the overexpression of Dr-WHy significantly enhanced the oxidative resistance by *E. coli* [22]. Collectively, the shortened HD domain of LEA3 and WHy domain of LEA5 are the core fragments for the oxidative resistance, which are functionally in line with the full-length ones. Critically, the functional domains from *D. radiodurans* performed much stronger excellent resistance than other proteins belonging to the same LEA groups [21].

3.3. Protection of LEA protein functions via a chaperone mechanism

Previously, LEA proteins were reported to protect LDH, an important metabolic enzymes for energy conservation, against freezing damage [64,65]. Recent studies showed that LEA proteins could also protect LDH from oxidation and desiccation respectively in addition to freezing damage [21,22,69]. Our published data also revealed the protective mechanism through which functional HD domains could effectively prevent LDH aggregation via high-affinity molecular interaction and thus the activity was maximally maintained at the occurrence of desiccation and oxidation stresses. Furthermore, DrHD from *D. radiodurans* displayed an excellent role in preventing the aggregation of LDH among the other HDs [21]. In addition, the studies of Dr-WHy domain of group LEA5 from *D. radiodurans* may similarly and effectively protect MDH and LDH activities from oxidative stress. However, the underlying molecular mechanism of how Dr-WHy domain in DR1372 function remains unknown. Collectively, these studies provide a reminiscence of the role of molecular chaperone action as stress protectants.

LEA proteins are proposed to act as chaperone-like or molecular shield mechanisms [70–72]. However, there are some intrinsic differences between LEA proteins and the classical chaperones heat shock proteins (HSPs), such as HSP90 and DnaK (HSP70). Most LEA proteins, except the group LEA5 proteins, are naturally disordered [46,71,73], while the HSPs are ordered apart from a disordered segment [74,75]. Furthermore, LEA proteins could recognize and bind directly to LDH and the aggregation of LDH was maximally inhibited, which prevented the enzyme's conformation from misfolding [21]. In addition, unlike the canonical chaperones, LEA proteins do not need additional ATP or carbohydrates, such as trehalose [76,77]. Taken together, we propose a working model of protection mechanisms against oxidation by LEA proteins as delineated in Fig. 4.

3.4. Other potential functions

As discussed above, recent understanding with *D. radiodurans* revealed that LEA proteins can bind a number of metal ions, including Mn^{2+}, Zn^{2+}, and Cu^{2+} [42], which was often in agreement with the earlier studies that group LEA4 proteins from soybeans can bind metal ions Fe^{3+}, Ni^{2+}, Cu^{2+} and Zn^{2+} [78]. The high proportion of histidine residues was assumed contributing to the metal-binding property and further the metal concentrations or ratios maintaining the ions homeostasis were regarded as one of antioxidant defense systems [79,80]. Although the biochemical identification illustrated the necessity of DR1172 to control the intercellular Mn/Fe ratio, the molecular work measuring the interaction of DR1172 and ions, and the affinity of their binding, remain to be unfolded. Interestingly, a novel LEA-like protein, anhydrin, was recently reported to possess an endonuclease activity to cleave supercoiled, linear, and chromatin DNA [81]. In summary, as many metal ions are crucial cofactors for enzymes to initiate their biochemical reactions, we hypothesized that the binding of metal ions to LEA proteins may not be limited to maintain the metal ions homeostasis and may have unknown functions, for instance, DR1172 may be able to activate the stress-inducible networks when cells are under harmful conditions.

Recently, DR1372 was also characterized to protect the host microbes from oxidation [22]. These important studies provide new insight into the function of group 5 LEA proteins and warrant further investigations into the structural and functional relationship. For example, the subcellular localization, which seems to be anchored into the cell membrane, may be an interesting topic as the LEAs bear hydrophobic domains that were inter-miscible with the hydrophobic peripheral membrane. Additionally, whether these domains and their interaction/localization in relation to their partners have the potential to maintain the metal ions homeostasis and the membrane integrity by protecting membrane integral proteins, remains unknown and needs further research.

4. Summary and outlook

In this review, we highlighted the current research progress of LEA proteins of the extremophilic *D. radiodurans*. Both DR1172 and DR1372 were biochemically and physiologically characterized in response to dehydration, especially oxidation and desiccation. Moreover, their truncated core HD heterologous expression, can significantly improve the host stress tolerance, providing effective genetic blocks to synthetic biology and food crops growing under adverse environments, such as desiccation. Molecular biology studies demonstrated that through a chaperone-like or molecular-shield mechanism, DR1172 can protect critical metabolic enzymes (e.g., LDH) that catalyze the lactate to pyruvate coupling to energy conservation. Furthermore, the subcellular localization of DR1172 indicates that this protein was functionally associated with membrane integrity [42]. Given that the LDH is

one of the important electron transport chain components, DR1172 may contribute to maintaining the energy metabolisms under stress conditions. In addition, metal ions are important cofactors for metalloenzymes, and DR1172 might protect enzymatic activity by maintaining metal ion homeostasis in addition to directly binding to the enzymes to avoid aggregation under stresses. Collectively, the LEA proteins in *D. radiodurans* play pleiotropic roles against extreme conditions, such as oxidation and desiccation. For instance, when co-expressed in a human cell line, the LEA protein AavLEA1 reduces the propensity of polyglutamine and polyalanine expansion proteins associated with neurodegenerative diseases to form aggregates, demonstrating *in vivo* function of an LEA protein as an antiaggregant [82]. Furthermore, the LEA proteins AfrLEA2 and AfrLEA3m can dramatically improve the survival of human cells during acute desiccation to low water conditions, such as spin-drying [83]. Thus, the LEA proteins from *D. radiodurans* may possess potential therapeutic and medical values for various pathophysiological conditions in humans. Importantly, when people face oxidative damages from infection, neuronal degeneration, space journey, high concentrations of oxygen and allergen exposure, DNA repair proteins may join the fold of anti-oxidation processes [84–88]. Whether the DNA repair pathways have a crosstalk with LEA proteins is unknown and may be an important future topic. We thus speculate that the LEA proteins may benefit human health by providing potential therapeutic values for various diseases, such as Huntington's disease, which is caused by aggregation-prone proteins.

CRediT authorship contribution statement

Yingying Liu: Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Chen Zhang:** Software, Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Zhihan Wang:** Investigation. **Min Lin:** Investigation. **Jin Wang:** Conceptualization, Writing - original draft, Writing - review & editing. **Min Wu:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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