MINI-REVIEW

New insight into the mechanisms protecting bacteria during desiccation

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Abstract

Desiccation is a common stress that bacteria face in the natural environment, and thus, they have developed a variety of protective mechanisms to mitigate the damage caused by water loss. The formation of biofilms and the accumulation of trehalose and sporulation are well-known strategies used by bacteria to survive desiccation. Other mechanisms, including intrinsically disordered proteins and the anti-glycation defence, have been mainly studied in eukaryotic cells, and their role in bacteria remains unclear. We have recently shown that the impairment of trehalose synthesis results in higher glucose availability, leading to the accumulation of acetyl phosphate and enhanced protein acetylation, which in turn stimulates protein aggregation. In the absence of trehalose synthesis, excess glucose may stimulate non-enzymatic glycosylation and the formation of advanced glycation end products (AGEs) bound to proteins. Therefore, we propose that trehalose may prevent protein damage, not only as a chemical chaperone but also as a metabolite that indirectly counteracts detrimental protein acetylation and glycation.

Keywords Advanced glycation end products · Desiccation · Protein acetylation · Protein aggregation

Introduction

The most common stress that bacteria face in the natural environment is water loss during desiccation. Dehydration results in the condensation of molecules and membrane disruption; reduction of the hydration shell around proteins leads to conformational changes resulting in the loss of enzymatic activity and denaturation. Due to inactivation of the antioxidant mechanisms, free radicals accumulate in the cell causing damage to DNA, proteins and lipids (Lebre et al. 2017). The loss of protein stability and increased molecular crowding favor destructive reactions, including non-enzymatic glycosylation (glycation or the Maillard reaction), leading to irreversible cross-linking and polymerization of proteins and nucleic acids (Boteva and Mironova 2019). Bacteria have elaborated multiple mechanisms that help them to withstand desiccation stress for extended periods. Outbreaks

of nosocomial infections are often caused by clinical isolates that can survive on dry surfaces in the hospital environment. Food-borne diseases may be caused by pathogens able to survive the procedures frequently used in the food processing industry, such as desiccation, freeze-drying or hyperosmolarity (Burgess et al. 2016; Lebre et al. 2017). Therefore, the understanding of mechanisms underlying bacterial desiccation tolerance is crucial for human health.

The best characterized strategies involve the formation of biofilms and spores, the accumulation of compatible solutes and synthesis of stress proteins, including molecular chaperones and proteins detoxifying reactive oxygen species. Several excellent reviews have been recently published on these topics (Burgess et al. 2016; Lebre et al. 2017; Esbelin et al. 2018; Vega-Cabrera et al. 2018). Therefore, we focus only on those selected mechanisms that protect proteins during desiccation stress.

Intrinsically disordered proteins

Late Embryogenesis Abundant (LEA) proteins that accumulate in the late stages of seed maturation were the first identified intrinsically disordered proteins (IDPs) involved in desiccation tolerance (Hincha and Thalhammer 2012).

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LEA proteins form molecular shields that occupy the space around denatured proteins and inhibit their aggregation (Chakrabortee et al. 2007). Recent studies indicate that IDPs are abundantly present in all proteomes analyzed to date. IDPs can also serve as molecular chaperones, scavengers of reactive oxygen species, hydration buffers or may participate in filament polymerization to maintain higher-order structures in the cell (Boothby and Pielak 2017; Janis et al. 2018). An interesting example of IDPs is the proteins found exclusively in extremotolerant tardigrades. These tardigrade-specific disordered proteins vitrify (form glasses) to reinforce structural integrity of the animal (Boothby et al. 2017). It has been suggested that vitrification protects macromolecules by trapping them within the pores of an amorphous matrix that prevents protein denaturation and aggregation (Boothby and Pielak 2017). Numerous studies have revealed that IDPs participate in a liquid–liquid phase separation (LLPS) of proteins, leading to the formation of dynamic membrane-less organelles, such as Cajal bodies, the nucleolus or stress granules in eukaryotic cells (Shin and Brangwynne 2017; Franzmann and Alberti 2019).

Bacterial proteomes are less disordered than eukaryotic proteomes (Darling and Uversky 2018). Nevertheless, according to the DisProt database [https://beta.disprot.bio.unipd.it (Piovesan et al. 2017)], over 80 E. coli IDPs have been identified to date. Moreover, the formation of membrane-less organelles in the cytoplasm and LLPS of bacterial proteins has been reported (Abbondanzieri and Meyer 2019, Monterroso et al. 2019, Al-Husini et al. 2018). It is worth noting that the intracellular environment of prokaryotes is denser than the eukaryotic cytosol, and the bacterial cytoplasm has properties that are characteristic of glass-forming liquids (Parry et al. 2014; Fonseca et al. 2016). Interestingly, it has been demonstrated that cytoplasm fluidity decreases when metabolic activity is inhibited, e.g., during the stationary phase, suggesting that after cytoplasm transition to a solid-like state, bacteria may enter dormancy (Parry et al. 2014). The glass transition of cytoplasm may affect particularly large cellular components, not only by inhibiting their motion but also by stabilizing their structures. A good example is the 100S ribosome which is a dimer of non-translating 70S ribosomes formed constitutively or during the late stationary phase and in response to various stress factors, depending on the bacterial species (Gohara and Yap 2018). Under favorable conditions, these so-called "hibernating ribosomes" disassemble allowing restart of translation. Both ribosome hibernation and the transition of the cytoplasm into a glass-like stage may contribute to the phenomenon of the enhanced ability of bacteria to survive desiccation during stationary phase (Potts 1994).

Trehalose and Nε-lysine acetylation

A characteristic feature of many anhydrobionts is the accumulation of soluble sugars, including non-reducing disaccharide trehalose (Jain and Roy 2009; Esbelin et al. 2018; Jiang et al. 2018). Trehalose acts as a chemical chaperone, stabilizes denatured proteins and facilitates their refolding in vivo and in vitro (Singer and Lindquist 1998; Diamant et al. 2001; Corradini et al. 2013; Tapia and Koshland 2014). Divergent models have been proposed to explain the protective functions of trehalose. According to the water replacement and exclusion theories, trehalose stabilizes proteins by the displacement of water molecules from their surfaces. The vitrification theory suggests that trehalose forms a viscous glass to shield proteins (Sussich et al. 2001; Crowe et al. 2002; Street et al. 2006; Jain and Roy 2009).

We have shown recently that the synthesis and storage of trehalose in E. coli prevent carbon stress, i.e., carbon overflow, which otherwise is manifested by protein acetylation and aggregation (Moruno Algara et al. 2019). The first step of trehalose synthesis is the formation of trehalose-6-phosphate from UDP-glucose and glucose-6-phosphate (Ruhal et al. 2013). In ΔotsA cells, unable to synthesize trehalose, the excess glucose-6-phosphate is converted into pyruvate and then into acetyl-CoA and acetyl phosphate (AcP). AcP is engaged in non-enzymatic Nε-lysine acetylation of hundreds of E. coli proteins (Kuhn et al. 2014; Wolfe 2016). Since AcP is generated in response to carbon overflow, it has been proposed that AcP may be used as a sensor for the nutritional status of the environment, and subsequent acetylation of proteins could limit carbon flux to optimize E. coli growth (Christensen et al. 2019). According to this, we observed increased accumulation of AcP and enhanced protein acetylation in ΔotsA cells. Since Nε-lysine acetylation neutralizes positively charged lysine-side chains and increases their size and hydrophobicity, acetylation stimulates protein aggregation. (Kuczyńska-Wiśnik et al. 2016; Moruno Algara et al. 2019). These results demonstrated that trehalose may protect proteins against aggregation as a metabolite that indirectly counteracts detrimental acetylation. It should be noted that while some eukaryotic proteins form aggregates after acetylation, others are stabilized in a soluble and active form. The effect of acetylation on aggregation propensity probably depends on the position of lysine-acetylated sites and their functional implications (Cohen et al. 2015; Olzscha et al. 2017; Ferreon et al. 2018).

An alternative mechanism of N-ε lysine acetylation in bacteria involves lysine acetyltransferases (KATs), which catalyze acetylation of specific lysines using acetyl-CoA as the acetyl donor (Christensen et al. 2018). It has been

reported that the impairment of KATs-dependent protein acetylation decreases bacterial tolerance to various harmful conditions, including oxidative and high-salt stress (Ma and Wood 2011; Castaño-Cerezo et al. 2014; Liu et al. 2018). These results suggest that protein acetylation mediated by KATs may be involved in desiccation tolerance; however, further studies are needed to confirm this presumption.

Recent reports indicate that acetylation may affect the structural and functional properties of eukaryotic IDPs (Darling and Uversky 2018). For example, Nε-lysine acetylation of the intrinsically disordered regions in DDX3X, an RNA helicase, inhibited LLPS and the assembly of stress granules (Saito et al. 2019); whereas, hyperacetylation of the microtubule-associated protein Tau disfavored LLPS and inhibited Tau aggregation (Ferreon et al. 2018).

Anti-glycation defence

Protein glycation (the Maillard reaction) has been studied mainly in eukaryotic systems due to its relation to aging and human diseases. However, there is increasing evidence indicating that protein and DNA glycation also occurs in bacteria despite their short life span (Mironova et al. 2001; Potts et al. 2005; Cohen-Or et al. 2013; Kram and Finkel 2015). Methylglyoxal (MGO) and glyoxal (GO), formed as the by-products of glycolysis or lipid peroxidation (Rabbani and Thornalley 2015), are responsible for up to 60% of glycation damage (Richarme et al. 2018). In the initial stage of the Maillard reaction, the aldehyde form of monosaccharides (glucose and fructose), MGO and GO react spontaneously with proteins (Fig. 1) and nucleic acids. Resulting adducts are sequentially transformed into Shiff's bases, Amadori products, and finally into advanced glycation end products
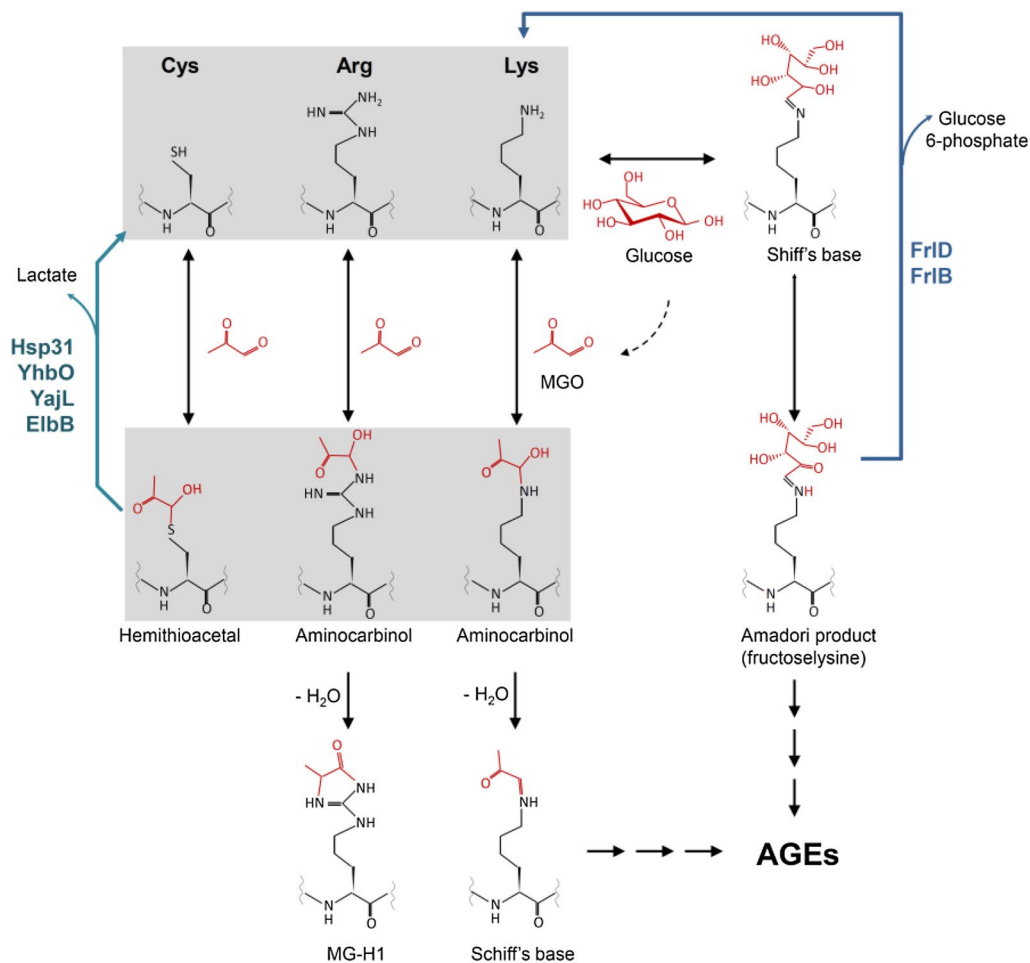

Fig. 1 Non-enzymatic glycosylation of proteins. In the initial stage of the Maillard reaction, the aldehyde form of monosaccharides (glucose and fructose) or the glycolytic by-products, such as methylglyoxal (MGO), react spontaneously with thiol and amino groups of proteins. Resulting aminocarbinols (with lysine and arginine) are transformed into Shiff's bases and next into more stable Amadori products. Advanced glycation end products (AGEs) are formed after additional rearrangements and glycoxidation. *E. coli* enzymes: Hsp31, YhbO, Yaj, ElbB, FrlB and FlrD catalyse deglycation of some adducts. *MGO* methylglyoxal, *MG-H1* hydroimidazolone

(AGEs) (Richarme et al. 2018; Boteva and Mironova 2019). AGEs are heterogeneous group of adducts that are prone to aggregation due to intra- and intermolecular crosslinks. Bacteria have developed diverse mechanisms preventing the Maillard reaction. MGO detoxification is catalysed by multiple enzymes including the glyoxylase I/II system, MGO reductase and a group of enzymes converting MGO into acetol. In *E. coli,* four deglycases: Hsp31, YhbO, YalL and ElbB degrade the initial Maillard adducts (Fig. 1). Because these proteins display chaperone activities, they may additionally participate in non-covalent protein repair (Richarme et al. 2018). *E. coli* also produces two enzymes FrlD and FrlB that have been shown to catabolise glycated lysines released upon digestion of food proteins in the human intestine (Wiame et al. 2002). Recent studies indicate that *E. coli* endogenous proteins are substrates for these enzymes: the FrlD kinase phosphorylates fructoselysine (the Amadori product of lysine glycation), whereas FrlB catalyzes the hydrolysis of Nε-fructoselysine 6-phosphate to lysine and glucose 6-phosphate (Fig. 1) (Atanasova et al. 2014). AGEs, the final products of glycation, are degraded by metalloproteases and secreted by the energy-dependent efflux pump systems (Cohen-Or et al. 2013).

Since both glycation and acetylation may occur on the lysine residue, it seems that these two types of modification compete with each other. Zheng et al. (2019) demonstrated that lysine acetylation protected histones from detrimental glycation in breast cancer cell line. It was also found that Nε lysine acetylation and AGEs formation co-occured in the eye lens molecular chaperones αA- and αB-crystallin (Nahomi et al. 2013). Prior acetylation of αA- and αB-crystallin in vitro before glycation with MGO resulted in significant inhibition of the synthesis of AGEs. Moreover, lysine acetylation prevented loss of chaperone activity of αA- and αB-crystallin caused by glycation.

Conclusions and perspectives

The findings presented above suggest that there is a potential interplay between trehalose synthesis and the acetylation and glycation of proteins in bacteria exposed to desiccation stress. We propose that detrimental acetylation and glycation of proteins may be reduced by trehalose synthesis (Fig. 2). This hypothesis is based partly on findings observed in eukaryotic cells, and further studies are needed to verify this model in bacteria. Nevertheless, we have found that in the absence of trehalose synthesis protein, acetylation and aggregation as well as the accumulation of AGEs are enhanced in desiccated *E. coli* cells (Moruno Algara et al. 2019, unpublished results). Both glycation and acetylation may occur on the lysine residue; therefore, it is tempting to speculate that lysine acetylation inhibits the formation of AGEs. This would be beneficial to the cell because
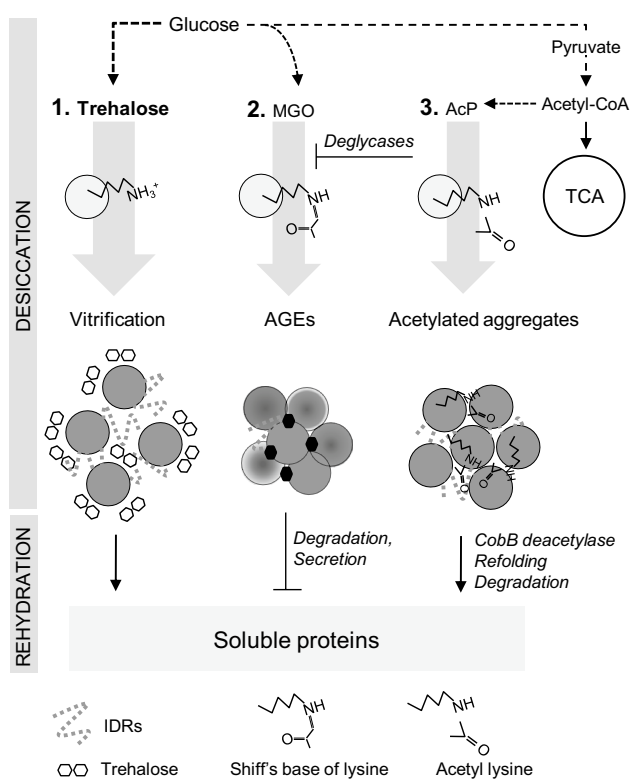
Fig. 2 Hypothetical model for the role of trehalose during desiccation. Trehalose protects proteins as a metabolite that indirectly counteracts detrimental protein glycation and acetylation. The lack of trehalose synthesis may result in higher glucose availability which in turn stimulates acetylation and glycation. (1) Trehalose and IDPs allow condensation and transition of soluble proteins into a glass-like state. (2) Protein glycation leads to the formation of AGEs and crosslinked aggregates. (3) AcP-dependent Nε-lysine acetylation neutralizes positively charged lysine side chains and increases hydrophobicity, which in turn, promotes protein aggregation. For clarity, vitrification, glycation and acetylation are shown separately, but all these processes may co-occur in the cell. During rehydration the protein condensates are transformed into a liquid state, the AGEs are degraded and secreted, acetylated and aggregated proteins are solubilized by deacetylation and refolding. *AcP* acetyl phosphate, *AGEs* advanced glycation end products, *IDPs* intrinsically disordered proteins, *MGO* methylglyoxal

acetylation is a reversible modification. In *E. coli,* the deacetylase CobB selectively deacetylates at least some acetyl lysines (Abouelfetouh et al. 2015). Therefore, proteins acetylated upon desiccation can be recovered from the aggregates by deacetylation and refolding; whereas, proteins irreversibly damaged by glycation must be synthesized de novo. In *E. coli*, protein aggregates are deposited at the cell poles due to nucleoid occlusion. In consequence, after cell division aggregates may be inherited only by one of the progeny cells (Winkler et al. 2010). A recent study has demonstrated that the cells inheriting aggregates show increased resistance to subsequent proteotoxic stresses, probably due to co-localisation of molecular chaperones with the aggregates

(Mortier et al. 2019). It is plausible that asymmetric segregation of protein aggregates also occurs during rehydration and re-growth of desiccated bacteria. The rapid uptake of water during rehydration may cause cell damage. The question, thus, arises as to which of the two progeny cells, the aggregate-bearing or the aggregate-free cell, is better adapted to the stress imposed by rehydration. The involvement of LPPS in protein aggregation in bacteria is another interesting issue that should be addressed. The aggregates formed in stressed *E. coli* cells contain ribosomal proteins and proteins involved in glycolysis, TCA cycle and other metabolic pathways (Moruno Algara et al. 2019). Some of these proteins possess intrinsically disordered regions; therefore, it is not excluded that the formation of liquid droplets via LLPS precedes aggregation. This hypothesis is consistent with the studies indicating that, with time, proteins concentrated in liquid droplets are converted into aggregates (Patel et al. 2015).

It is worth noting that phase separation of proteins and vitrification of the cytoplasm caused by water loss may induce a dormant state (Parry et al. 2014). Dormant bacteria are difficult to be detected by standard microbiological methods and often acquire antibiotic tolerance. Therefore, the understanding of mechanism underlying tolerance to desiccation stress may help to improve or develop new antibacterial strategies.

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