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Trehalose: As Sweet as Effective in Biomedical Research and Biotechnology

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Abstract

Since the trehalose discovery, this disaccharide has been reported to accumulate in anhydrobiotic organisms which are able to survive completely dry and dormant until living conditions improve. Trehalose has been widely studied to understand its function and abundance in nature due to its unique features, including the ability to sustain and preserve a wide array of biological molecules. In face of these physical and chemical properties, this sugar has been used in a variety of food, medical and cosmetic products as well as in many biomedical researches. Currently, there is a growing interest in the use of trehalose as a relevant therapeutic agent in neurodegenerative disorders such as Alzheimer's, Huntington's and Parkinson's diseases as well as in the modification of trehalose molecule into novel inhibitors of cancer cell migration and invasion. These current applications have proven possible because of the trehalose ability to enhance autophagic activity, respond against a variety of environmental stressors and stabilize protein folding mechanisms. This brief review highlights the promising biotechnological and biomedical applications of trehalose.

Keywords: Trehalose; Microorganisms; Biotechnology

Abbreviations: T6P: Trehalose-6-Phosphate; Tps1: Trehalose synthase; Ath1: Acid trehalase; HD: Huntington's disease; PD: Parkinson's disease; AD: Alzheimer´s Disease; ROS: Reactive Oxygen Species; PoliQ: Polyglutamine; LBD: Lewy body disease; APP: Amyloid Precursor Protein; ER: Endoplasmatic Reticulum; OTSA: Trehalose-6-phosphate synthase

Introduction

Trehalose is a non reducing disaccharide composed of two residues of glucose joined through 1,1-α,α-glycosidic linkage [1,2]. This sugar is found in bacteria, fungi, plants, insects, and invertebrates, but not in vertebrates [3,4]. Humans have the ability to hydrolyze but not to synthesize treahlose. The main functions of trehalose are to confer protection against stress and to serve as fuel reserve [5]. The first recorded information of trehalose was in cocoons of Larinus beetles in 1681, and in 1953, Leloir and Cabib elucidated for the first time the complete metabolic pathway of trehalose. Trehalose can be biosynthesized by five pathways. It can be produced by the trehalose-phosphate synthase/trehalose phosphatase pathway in yeast, bacteria, archaea, insects, and plants.

Archaea, like *Hyperthermophilic archeae, Pyrococcus horikoshii, Thermococcus litoralis, Thermoproteus tenax* can also convert glucose and UDP-glucose into trehalose using trehalose-synthesizing glycosyltransferase [6]. Through the TreY/TreZ pathway Sulfolobus and Mycobacterium can convert malto oligosaccharides into trehalose [2]. Malto oligosaccharides and maltose can also be converted to trehalose by the trehalose synthase pathway in some bacteria [7]. The fifth biosynthetic pathway converts glucose and glucose-1-phosphate in trehalose using trehalose phosphorylase in bacteria, yeast and fungi, for example *Bacillus stearothermophilus*, T*hermoanaerobacter brockii* and *Copelatus subterraneus* [6]. In face of the interesting properties of trehalose, its role and metabolism have been investigated since a long time. However, there are still questions to be answered. Recently, Arthrobacter was used as a model to analyze development switches caused by the environment. This is possible because of its resistance to stress, probably related to their pleomorphic behavior. Trehalose-6-phosphate synthase (otsA) of Arthrobacter is probably involved in cellular morphology, representing an adaptation of bacteria that survive in extreme environments [8].

The protective effect of trehalose on *Rhodobacter sphaeroides* has also been presented. It was shown that a trehalose matrix

is able to protect the centers reactions of photosynthetic protein complexes against dehydration, leading to a greater maintenance of its photochemical activity [9]. *Saccharomyces cerevisiae*, *Candida albicans*, and *Candida Tropicalis* were used as experimental models to show the ability of Trehalose-6-Phosphate (T6P) to inhibit trehalose synthase (Tps1) activity. In this way, T6P reduced the trehalose synthesis that is directly related to the virulence of some pathogens [10]. The protective effect of trehalose on *Aureobasidium subglaciale*, a fungus collected on soil contaminated with radiation and heavy metals, has already been demonstrated. In this study, a strain with three fold higher trehalose production, due to overexpression of Tps1 and the deletion of acid trehalase (Ath1), showed greater resistance against heavy-metal and radiation than the control strain. This data leads to the conclusion that there is a relationship between trehalose accumulation and the oxidative stress response in *Aureobasidium subglaciale* [11]. Subheading: Biotechnology Applications of Trehalose More than a decade after the liberation of the use of trehalose in humans by the United States and the European Union, which classified trehalose as safe, the studies about this sugar are increasingly focused on its beneficial properties for humans [12]. Those properties are mainly related to the trehalose structure, specifically on the interaction between the two molecules of glucose and its function as a kosmotrope [13]. These properties are important for the protective roles against stress, as oxidative stress, heating and starving. Furthermore, trehalose is synthetized in a wide range of organism, other than humans, which lack TPS enzyme, necessary for trehalose production [5]. Since trehalose is able to stabilize the structure of biomolecules (proteins, enzymes, DNA) and macrostructures (lipid bilayer) and to avoid protein aggregation during denaturating conditions, it has been intensively investigated for application in the treatment of infectious diseases, caused by pathogens whose virulence depend on trehalose synthesis, neurodegenerative diseases and cancer [10,14]. On the other hand, some groups are developing methodologies to introduce trehalose in different areas, as cosmetics (development of bath oils, moisturizers, due to its role as protection against dehydration); pharmaceutical applications (as component in medicines to treat high blood pressure, due to its role to protects against osmotic stress) [14]. Trehalose can be found in some methods to produce and preserve dried vegetables and fruits, in the production of Swiss cheeses and as sweetener [15,16]. One of the problems faced during therapeutic treatment, which use drugs that need to be delivered inside the organism, is how to introduce this component without side effects to the organism and with high rates of absorption. An alternative for oral delivery and parenteral methods is the use of biodegradable microneedles. Some studies are focused in the use of trehalose during the creation of these needles due to its capacity of interaction with the biomolecules, producing a sugar glass layer, and then, protecting the structure against composition alterations during its development before their use in humans [17].

Due to its cryoprotective and preservative role, trehalose can be found in solutions of organs transplantation, development of vaccines, antibodies, and during skin treatment with anti-inflammatory drugs, where trehalose is used to reduce the side effects, as cutaneous irritation [15,18].

Trehalose as a therapeutic candidate ready to enter clinical trials

Trehalose also displays a number of remarkable qualities including the ability to protect the integrity of cells against desiccation, heat, cold and oxidation(5). Moreover, trehalose may act as a chemical chaperone, preserving protein structure stability, protein folding as well as reducing aggregation of pathologically misfolded proteins [19,20]. Oxidative stress, aggregation and proteasomal dysfunction have been considered key mechanisms associated with neurodegenerative disorders, including Huntington's disease (HD) [21], Parkinson's disease (PD) [22] and Alzheimer´s disease (AD) [23,24]. It was recently reported the treatment with trehalose was able to counteract the increase in reactive oxygen species (ROS), ubiquitinated proteins, huntingtin and activated caspase-3 levels induced by the inhibitor of proteasome activity epoxomicin. The authors also pointed out the valuable effects of this disaccharide in proteinopathies, as an autophagy enhancer, chemical chaperone, antioxidant and an interesting therapeutic candidate for testing in HD patients [21].

By using *in vitro* and *in vivo* models of HD, other studies have shown the trehalose was able to inhibit polyglutamine (poliQ) mediated aggregation [25,26]. Recent studies demonstrate that trehalose protects dopaminergic neurons in the striato-nigral pathway from the pathological symptoms induced by MPTP (eg. vessel regression and ischemia) in mouse models of Parkinson´s disease [27]. Other study currently highlighted the ability of the autophagy enhancer, trehalose to protect against A53T α-synuclein mediated dopamine degeneration in a rat model of PD [28]. Trehalose intake has increased levels of chaperone molecules, such as Hsp 90 and SigmaR1 along with autophagy in brains of model mice of Lewy body disease (LBD). It has also been reported in this study that oral administration of trehalose suppressed the levels of detergent-insoluble α-synuclein in mice [29]. As such, in Alzheimer´s disease, trehalose promotes the cellular clearance of the phosphorylated pathogenic tau protein [30-32]. In addition, cell treatment with trehalose was capable to alter vesicular trafficking, thereby decreasing the degradation of Alzheimer-associated Amyloid Precursor Protein (APP) in endolysosomal compartments and the secretion of amyloid-β peptide [33]. The role of trehalose in reducing Aβ peptide aggregation is still unclear, however a very recent study concluded that trehalose affects the conformation of Aβ peptide to form α-helical structure, which may prevent the formation of β-sheets and thereby aggregation [34].

The autophagic effects of trehalose together with its anti-apoptotic property on tumor cells and lack of toxicity on

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normal cells has been recently used as a Potential neoadjuvant for antitumor drugs for treating several cancers [35]. Other medically property of trehalose include the suppression of the osteoarthritis (OA) [36], herpesviruses [37] and age-associated liver injuries [38] mainly through the elimination of oxidative stress, reduction of endoplasmatic reticulum (ER) stress and autophagic flux restoration [36].

Conclusion

Since trehalose's discovery, this disaccharide has been widely studied due to its interesting and unique properties. It was formerly focused on the better understanding of the pathways of synthesis and its role in the microorganisms that synthesized it. In the last decade, research involving trehalose has increased focusing on its application in the food, pharmaceutical, and cosmetics industry. Based on the results obtained so far using different models, and the advance of new research techniques, more studies are on the way to find more applications of this interesting and versatile sugar.

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