Mechanistic Insight into Biotransformation of Inorganic Selenium to Selenomethionine and Selenocysteine by *Saccharomyces boulardii*: *In-silico* Study

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Abstract: In recent years, the biosynthesis of seleno amino acids from inorganic selenium has been a subject of investigation. *Saccharomyces cerevisiae* has been reported to bioaccumulate selenium through the metabolism of selenate. Different authors have postulated a metabolic pathway in which selenate is converted into selenomethionine or selenocysteine based on the research carried out so far. However, little has been known how other types of yeast achieve this bioconversion. For that reason, and due to the importance of *Saccharomyces boulardii* as a probiotic yeast, the present study proposes a biosynthetic route used by this yeast to incorporate inorganic selenium into organoselenium compounds. A comparative in-silico study was carried out using *Saccharomyces boulardii* ASMI41397V1 and a metabolic model at the genomic scale of *Saccharomyces cerevisiae* S288C. Basic local alignment database BLASTp-NCBI was used to identify orthologous genes in both strains, and the generated data were visualized in a circular layout using CIRCOS software. The metabolic route of selenium assimilation was proposed based on the obtained results.

Keywords: selenium; *Saccharomyces boulardii*; selenocysteine; selenomethionine; probiotic.

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1. Introduction

Yeasts can permanently incorporate ions found in their natural environment into their cellular structures [1]. In the recent decade, selenium enrichment in yeasts has been intensively investigated, and the most studied species include *Saccharomyces boulardii, Candida utilis, Yarrowia lipolytica, Kluyveromyces marxianus, Rhodotorula glutinis* [2-9]. The focus has been placed on the yeast's metabolism and their biotransformation capability to incorporate inorganic selenium into proteins, particularly enzymes [1]. Bioaccumulated selenium's concentration varies between species and can reach up to 5.64 mg of selenium/g d.w. of yeast in *Saccharomyces cerevisiae* and 1.64 mg of selenium/g DW of yeast in *Candida utilis* [10].

As for *Saccharomyces boulardii* was originally isolated from the lychee fruit and has been the only probiotic yeast approved by the Food and Drug Administration (FDA) for human
consumption [11,12]. *Saccharomyces boulardii* has been commonly used to prevent or treat severe diarrhea associated with bacterial infections and other gastrointestinal disorders [12]. In addition to probiotic properties [13], *Saccharomyces boulardii* has been reported to produce selenium nanoparticles [14]. Therefore, the yeast-assisted production process of organic selenium has been considered a green technology [14,15].

Nevertheless, few works have been focused on applying *Saccharomyces boulardii* to produce selenomethionine (SeMet) and/or selenocysteine (SeCys). The capacity of this yeast to synthesize selenoamino acids offers the possibility to gain access to selenium in a more bio-available and less toxic way [16, 17].

Previous studies have demonstrated similarities between the biosynthetic pathway of sulfur and selenium. The latter was found to replace sulfur and is incorporated in cells as SeMet and/or SeCys [1, 18]. Another proposed mechanism known as trans-sulfuration involves an unspecified enzymatic route that has not been proven yet [19]. Interestingly, not all the yeasts synthesize both selenoamino acids. In the case of *Saccharomyces cerevisiae* BY4741, it is also known that methionine is produced through a route different from the incorporation of inorganic sulfur [19]. In this context, it is possible that certain genes that encode enzymes expressed by *Saccharomyces cerevisiae* to synthesize organoselenium compounds could be orthologous to those found in *Saccharomyces boulardii*. Moreover, the genome of *Saccharomyces cerevisiae* has been the most studied and characterized among eukaryotes [20]. Therefore, the present *in-silico* study focused on identifying probable orthologous implied genes implied in the biosynthesis of organic selenium by *Saccharomyces boulardii* ASM141397v1 to propose a bioconversion route of sodium selenate into SeMet and SeCys.

2. Materials and Methods

2.1. Identification of the study object.

The genetic comparison was carried out using an *in-silico* study. *Saccharomyces boulardii* ASM141397v1 was selected as a study object compared to the *Saccharomyces cerevisiae* s288c genome due to the high genetic similarity between the two yeasts. The iMM904 model [21] and Kegg model [22] for *S. cerevisiae* were used to carry out a genetic comparison. The genetic information of both yeasts was retrieved from the NCBI database [23].

2.2. Bioinformatic search.

Genes involved in the production of SeMet and SeCys were identified using the Entrez database provided by NCBI [23]. Gene sequences reported in selenium metabolism were searched for *Saccharomyces cerevisiae* s288c. A similar procedure was carried out for *Saccharomyces boulardii* ASM141397v1. Sequences for orthologs identification were prepared.

2.3. Orthologs.

With the information collected, orthologs were searched using the BLAST server at the NCBI [23, 24]. BLASTp (protein-protein BLAST) program was selected, and the query sequence was submitted in FASTA format. In addition, the sequence alignment was carried out exclusively with *S. cerevisiae* s288c to compare and find local sequences similarity regions.
between the two strains [25]. A total number of 9361 amino acids were analyzed, and the data were visualized on a circular plot using Circos software that permitted exploring the genetic relationship between the two species (http://circos.ca/).

2.4. Construction of Metabolic Route.

Following the analysis of genetic homology, a metabolic route of selenium assimilation and the consequent production of SeMet and SeCys by *Saccharomyces boulardii* were postulated, considering previous proposals made by previous proposals Kieliszek *et al.* [26] and Asghari-Paskiabi *et al.* [27] for *S. cerevisiae*.

3. Results and Discussion

3.1. Bioinformatic search.

Biotransformation of selenate into organic selenium begins with the detoxification process that yeast performs in response to the excess of sodium selenate.

**Table 1.** Genes involved in the biotransformation of selenate into selenoamino acids in *Saccharomyces cerevisiae* s288c and *Saccharomyces boulardii* ASM141397v1.

| Gene   | Chromosome | locus_tag *Saccharomyces cerevisiae* s288c | locus_tag *saccharomyces boulardii* ASM141397v1 | Enzyme expressed                                           |
|--------|------------|---------------------------------------------|-------------------------------------------------|----------------------------------------------------------|
| SUL1   | II         | YBR294W                                     | AB282_00450                                     | High-affinity sulfate permease of the SulP anion transporter family |
| SUL2   | XII        | YLR092W                                     | AB282_03394                                     | High-affinity sulfate permease                             |
| MET3   | X          | YJR010W                                     | AB282_02749                                     | ATP sulfurylase                                            |
| MET14  | XI         | YKL001C                                     | AB282_03058                                     | Adenylylsulfate kinase                                     |
| MET16  | XVI        | YPR167C                                     | AB282_05395                                     | 3'-phosphoadenylsulfate reductase                          |
| MET10  | VI         | YFR030W                                     | AB282_01793                                     | Subunit alpha of assimilatory sulfite reductase            |
| MET17  | XII        | YLR303W                                     | AB282_03569                                     | O-acetyl homoserine-O-acetyl serine sulthrylase            |
| MET6   | Va         | YER091C                                     | AB282_01662                                     | Cobalamin-independent methionine synthase                  |
| SAM1   | XII        | YLR180W①                                   | AB282_03468                                     | S-adenosylmethionine synthetase                            |
| SAM2   | IV         | YDR302C                                     | AB282_00999                                     | S-adenosylmethionine synthetase                            |
| SAH1   | Va         | YER043C                                     | AB282_01610                                     | S-adenosyl-L-homocysteine hydrolase                        |
| CYS4   | VII        | YGR155W                                     | AB282_01996                                     | Cystathionine beta-synthase                                |
| STR3   | VII        | YGL184C                                     | AB282_02293                                     | Peroxisomal cystathionine beta-lyase                       |
| CYS3   | I          | YAL012W                                     | AB282_00053                                     | Cystathionine gamma-lyase                                  |
| STR2   | X          | YJR130C                                     | AB282_02643                                     | Cystathionine gamma-synthase converts cysteine into cystathionine |
| GSH1   | X          | YJL101C                                     | AB282_02849                                     | Gamma glutamylcysteine synthetase                          |
| GSH2   | XV         | YOL049W                                     | AB282_04624                                     | Glutathione synthetase                                     |

The metabolic pathway resembles the bioconversion route of sulfur in producing sulfur amino acids. In this pathway, selenium replaces sulfur and is incorporated in the chemical structure of methionine and cysteine [18]. According to Lazard *et al.* [28], genes implied in the biotransformation of selenate into SeMet and SeCys for *Saccharomyces cerevisiae* have been shown in Table 1. The reported genes were included in the search query of genetic sequence in *S. boulardii*. Although the identified genes for *S. boulardii* have received putative names, the encoded enzyme has the same function in both species.
3.2. Orthologs.

Once the relevant genes in *S. boulardii* were identified, homology analysis was carried out to verify whether the genes were orthologous in both strains [24]. The results were visualized on a circular plot, as shown in Figure 1, to determine orthologs in *S. boulardii* and *S. cerevisiae*. Seventeen genes were arranged ascending to the left according to the number of amino acids analyzed. On the right side, the two yeasts species *S. boulardii* and *S. cerevisiae* can be found. Each gene is homologously linked to *S. cerevisiae* (blue) and *S. boulardii* (green). In agreement with the BLASTp search results, they encode the same enzymes that have the same function. For that reason, *S. boulardii* can biosynthesize organoselenium compounds in the same way as *S. cerevisiae* does. The main difference was observed for SAH1 and MET6 genes which are found in chromosome V of *S. cerevisiae* and chromosome Va in *S. boulardii*.

Despite the high homology between the two genetic sequences, *S. boulardii* has unique physiological and metabolic properties, such as resistance to temperature and acid stress [29, 30]. Another distinctive characteristic is the absence of the following genes in the genome of *Saccharomyces boulardii* ASM141397v1: hexose transporter genes (*HXT11, HXT9*), genes implied in asparagine catabolism (*ASP3*-1, *ASP3*-2, *ASP3*-3, *ASP3*-4), transporter gene *ARN2*, genes involved in the biosynthesis of thiamine or pyridoxine (*SNZ2, SNZ3*), and metallothionein gene *CUP1* [31]. Nevertheless, none of these genetic differences affects the *S. boulardii* capacity to transform inorganic selenium into selenoproteins, produce selenoparticles and reduce to elemental selenium in detoxification processes.

![Figure 1](https://biointerfaceresearch.com/)  
**Figure 1.** The circular plot of orthologs identified for *Saccharomyces boulardii* ASM141397v1 (green) and *Saccharomyces cerevisiae* s288c (blue).

3.3. Biosynthetic route of SeMet and SeCys in *S. boulardii* ASM141397v1.

Based on the search results for genes implied in the biotransformation of selenium and information retrieved from the KEGG/PATHWAY database [22] combined with the available
reports on biotransformation of selenium by *S. cerevisiae* [26, 27], a biosynthetic pathway of selenoamino acid production by *S. boulardii* was proposed.

Assuming that biosynthesis starts with detoxifying selenium through a metabolic pathway similar to that of sulfur, the following beginning of absorption is proposed. Selenium could be absorbed in two different ways. The first one involves sulfur ABC membrane transporters encoded by operon cysAWTP. In this mechanism, selenium ions are transported using the energy derived from the hydrolysis of bound ATP. The second system comprises the enzymatic transport of selenium by sulfate permeases [26], encoded by AB282_00450 and AB282_03394 operons. These enzymes are involved in transferring selenite through the plasmatic membrane from the cell's exterior.

Once the selenite is found inside the cell, biotransformation begins with selenate activation. This process is carried out in two subsequent reactions. In the first step, the adenosyl-phosphoryl residue of ATP is transferred to selenate in a reaction catalyzed by ATP sulfurylase that AB282_02749 encodes. As a result, adenylyl selenate is produced, which in turn undergoes phosphorylation to 3’-phosphoadenylyl selenate in a reaction catalyzed by an adenyl-sulfate kinase (AB282_03058). Activated selenate is reduced to selenite prior to the biosynthesis of SeMet and SeCys. First, 3’-phosphoadenylylsulfate reductase (AB282_05395) catalyzes the reduction of 3’-phosphoadenylyl selenate to 3’,5’-bisphosphate, and free selenite, using reduced thioredoxin as substrate. Next, the assimilatory sulfite reductase alpha subunit (AB282_01793) converts selenite into hydrogen selenide. The latter is transferred to selenohomocysteine in the presence of O-acetylserine-O-acetylhomoserine sulfhydrylase (AB282_03569).

Biosynthesis of SeMet from selenohomocysteine is catalyzed by cobalamin-independent methionine synthase (AB282_01662). In this reaction, selenohomocysteine undergoes methylation necessary for SeMet formation. It has been observed that activation of methyltransferases is a cobalamin-dependent reaction similar to that of MetH isolated from *E. coli* [32]. However, homocysteine methyltransferase found in *S. cerevisiae* and *S. boulardii* is a cobalamin-independent enzyme. It has been verified that B12 was not required for these yeast strains to grow.

Moreover, SeMet is converted to S-adenosyl-selenomethionine through the action of S-adenosylmethionine synthetase (AB282_03468/AB282_00999) that catalyzes the transfer of an adenosyl group of ATP to the selenium atom of selenomethionine. In the next step, S-adenosyl-selenomethionine is transformed into S-adenosyl-selenohomocysteine upon the action of methyltransferase. Selenohomocysteine is released again in a reaction catalyzed by S-adenosyl-L-homocysteine hydrolase (encoded by AB282_01610) that catabolizes S-adenosyl-L-homocysteine. The latter is formed following the donation of the activated methyl group of S-adenosyl-L-methionine (AdoMet) to a receptor. Substitution of methionine by SeMet in proteins does not significantly alter the kinetic properties of the enzymes [17].

As for the biosynthesis of SeCys from selenohomocysteine begins with the conversion of selenohomocysteine to selenocystathionine in a reaction catalyzed by cystathionine β-synthase (encoded by AB282_01996). Since the reverse reaction is catalyzed by peroxisomal cystathionine β-lyase (AB282_02293), selenocystathionine is converted back to selenohomocysteine. The next step consists of selenocystathionine transformation to SeCys in the presence of cystathionine γ-lyase (AB282_00053). Furthermore, γ-glutamyl-selenocysteine catalyzes the transformation of SeCys to γ-glutamyl-selenocysteine which is the first step in the biosynthesis of selenogluthathione. Finally, selenogluthathione is produced in the reaction of
\(\gamma\text{-glutamyl-selenocysteine}\) and glycine catalyzed by an ATP-dependent glutathione synthetase (AB282_04624), as shown in Figure 2. The sulfur amino acids pathway is correlated with the synthesis of selenocysteine and selenomethionine in yeast such as *Saccharomyces* species [33].

**Figure 2.** Biosynthetic pathway of organic selenium proposed for *Saccharomyces boulardii* ASM141397v1

### 4. Conclusions

Identification of orthologs between *S. cerevisiae* and *S. boulardii* permitted determining the biochemical route used by the probiotic yeast to convert inorganic selenium into selenomethionine and selenocysteine. *In-silico* studies have been used to gain theoretical insight into the biochemical mechanisms that govern *S. boulardii*. These biotransformations are of great relevance for technological applications. The addition of *S. boulardii* during the processing of fermented foods offers advantages that go beyond the proven probiotic capacity. Recent studies have shown the importance of organic selenium as a metabolite of high bio-accessibility and bioavailability in the human body compared to the commonly consumed inorganic selenium. Finally, the ability of *S. boulardii* to accumulate selenium could be used in the production of seleno nanoparticles, which have a vast potential of applications including medicine, such as alternative therapies in the fight against cancer, among others.

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Conflicts of Interest

The authors declare no conflict of interest.

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