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SULPHUR ASSIMILATION PATHWAYS IN MODEL EUKARYOTES- A REVIEW

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ABSTRACT: Sulphur is an essential nutritional requirement for all living organisms. Sulphate assimilation pathway has been considered quite significant as it is the source of reduced Sulphur for various cellular processes and for the synthesis of glutathione. Different organisms assimilate Sulphur through different pathways and mechanisms. Sulphur assimilation is largely confined to plants like *Arabidopsis* and microorganisms particularly *E.coli* since higher eukaryotes are unable to assimilate inorganic sulfur and therefore must rely on ingested methionine and cysteine. Microbes can reduce sulfate, thiosulfate or elemental sulfur while the higher plants use sulfate for amino acid synthesis. With the advent of Comparative Genomics, several genome wide studies are in pipeline to facilitate the understanding of metabolic pathways in different organisms. In this study, the Sulphur assimilation pathway in *Saccharomyces cerevisiae* has been reviewed and also some aspects of the pathways of *Arabidopsias thaliana* and humans to highlight the differences and similarities between these pathways have been discussed.

KEYWORDS: Sulphur, Sulphur assimilation pathway, Comparative Genomics, Methionine

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1.INTRODUCTION

Sulphate assimilation pathway is used by prokaryotes, fungi and photosynthetic organisms to convert inorganic sulphates to sulfide, which is incorporated into carbon skeletons of amino acids to form cysteine or homocysteine. Sulfur assimilation pathway leads to the formation of hydrogen sulfide, a precursor in the biosynthesis of homocysteine, cysteine and methionine [1]. Our knowledge about the molecular mechanisms and regulation of sulphate assimilation lags behind

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that of assimilation of carbon and nitrogen. Nevertheless, during the last few years considerable progress has been made in understanding its assimilation.

Sulphur assimilation has been intensively investigated by –omics technologies and has been target of several genome wide genetic approaches. This brought a significant step in our understanding of the regulation of the pathway and its integration in cellular metabolism [2]. Sulphur assimilation has been extensively studied in the model yeast *Saccharomyces cerevisiae* [3]. Extensive genetic, molecular, and biochemical studies with this yeast have led to a very good understanding of the sulfur assimilation pathways in this organism. The other well-studied eukaryotes include the model plant, *Arabidopsis thaliana* [4] and humans [5]. Among prokaryotes the Sulphur assimilation pathways have been investigated intensively in the gram-negative bacteria *Escherichia coli* [6] and the gram-positive bacteria, *Bacillus subtilis*. The Sulphur assimilatory pathway of *S.cerevisiae* has been intensively investigated over the last several years leading to a detailed understanding of the pathway of sulphate assimilation and reduction, as well as direct assimilation and metabolism of reduced sulfur compounds. This is schematically shown in Figure 1.

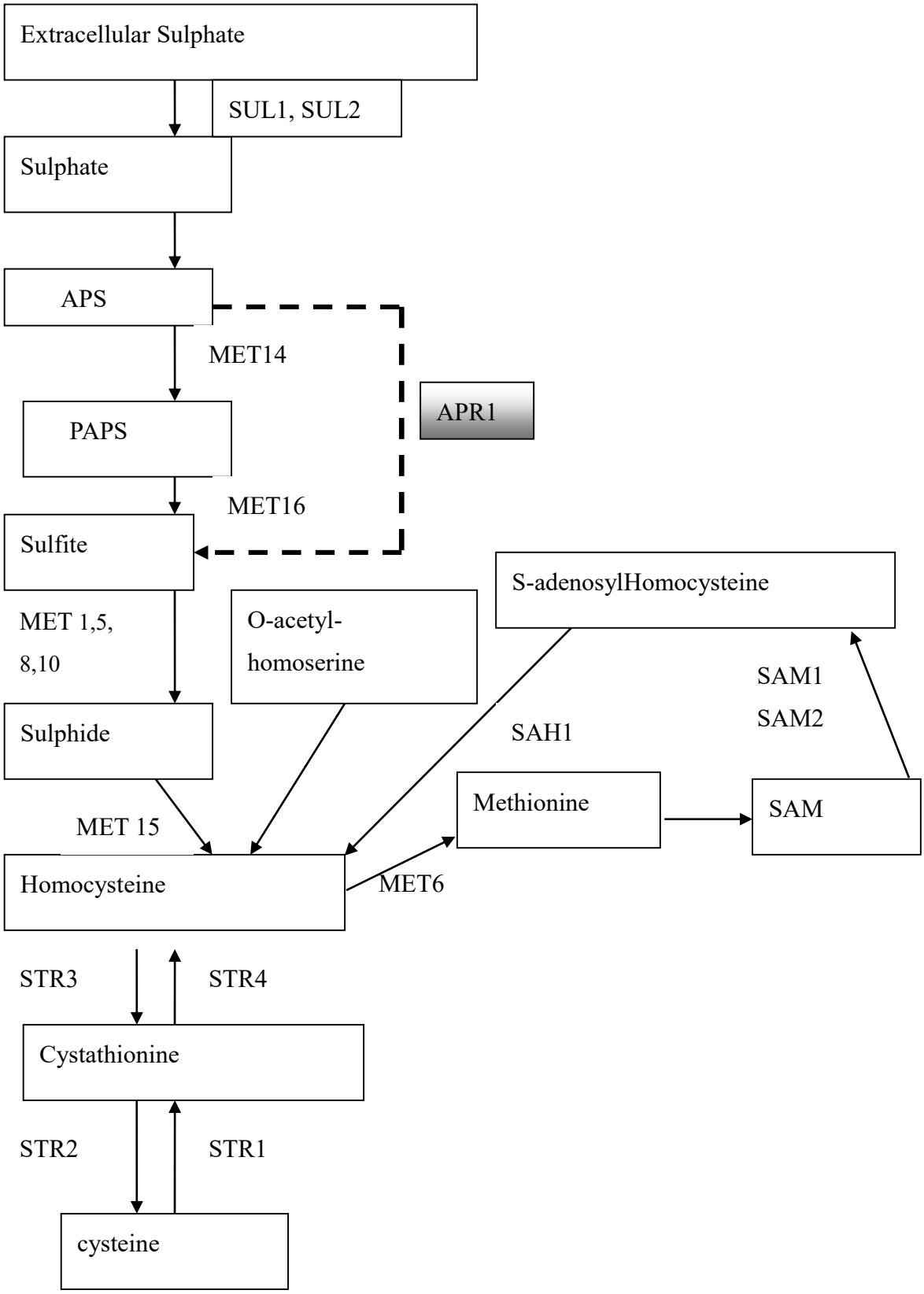

Figure 1. Sulphur assimilatory pathway of *Saccharomyces cerevisaiae* also showing the Bypass pathway present in Plants (APS reductase, APR1)

In *S.cerevisiae,* sulphate can be taken by two closely related transporters (SUL1, SUL2) specific for sulphate[7]. Once inside the cell, the sulphate is eventually reduced by the sequential action of different enzymes. In the first step, sulphate is activated by the transfer of adenosyl-phosphoryl moiety of ATP to sulphate by the ATP sulphurylase enzyme (MET3) yielding adenyl sulphate (APS) [8]. This gets phosphorylated further to yield phosphoadenylyl sulphate (PAPS) by APS kinase enzyme (MET14). For cysteine and methionine biosynthesis, activated sulphate is first reduced to sulphite by the enzyme PAPS reductase (MET16), which is in turn further reduced to sulphide by sulphite reductase (MET1, ECM17, MET 8, MET 10). Sulphide then gets incorporated into homocysteine via the enzyme homocysteine synthase (MET17). MET2 which encodes the enzyme homoserine trans-acetylase forms O-acetyl homo-serine. O-acetyl homo-serine conjoins with sulphide to form homocysteine, a reaction catalyzed by homocysteine synthase (MET17) as described above. Homocysteine can be converted into methionine by the enzyme homocysteine methyltransferase (MET6). Homocysteine can also be channeled to cysteine via the formation of cystathionine by the sequential action of two enzymes: Cystathionine β-synthase (CYS4) and Cystathionine γ -lyase (CYS3). Cysteine can also be converted back to homocysteine via Cystathionine-γ-synthase (STR2) and cystathionine β-lyase (STR3), just as methionine can be converted back to homocysteine via S-adenosylmethionine synthase (SAM1, SAM2) and S-adenosyl homocysteine synthase (SAH1). The interconversion of homocysteine to cysteine and methionine occurs by enzymes that are known as “transsulpuration enzymes”. These enzymes are Pyridoxal 5’-phosphate (PLP) dependent enzymes and are characterized by the presence of a common sequence domain. In addition to assimilation of Sulphur via reduction of sulphite, *S. cerevisiae* can also assimilate cysteine, methionine, homocysteine, or glutathione, which can be converted to other amino acids by the transsulphuration enzymes. Each of the organic Sulphur compounds are taken up by specific transporters. Thus, cysteine and homocysteine are taken up predominantly by YCT1 [9], methionine by MUP1 [10] and glutathione is taken up by HGT1[11]. Although chemotrophic bacteria and fungi utilize PAPS for reduction to sulphite in a reaction catalyzed by the thioredoxin-dependent PAPS reductase described above (Encoded by MET16 in *S.cerevisiae*), photosynthesizing organisms like plants and cyanobacteria have been shown to contain an alternative reductive pathway. In these organisms, instead of reduction of PAPS, these organisms have the ability to reduce APS, 5’-phosphosulphate (the precursor to PAPS) directly to sulphite through the action of an enzyme, APS reductase. The APS reductase is a glutathione-dependent enzyme. Thus, in *Arabidopsis thaliana,* the alternative enzyme, APS reductase encoded by Adenosine 5'-Phosphosulfate Reductase (APR1) converts APS to sulphide [12]. The APS reductase enzyme is not present in yeasts or other bacteria that use the PAPS reductase enzyme. The PAPS generated in plants and cyanobacteria is used mostly as a source of active sulphate for sulphation of proteins, metabolites through the action of sulphotransferases.[13]

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In humans the reductive pathway of sulphate assimilation has been found to be absent. Thus, neither PAPS reductase nor APS reductase is present in humans. Reduced Sulphur is obtained through the Sulphur containing amino acids. Methionine is a dietary indispensable amino acid in humans. Methionine that is taken up can be converted to cysteine through a series of transmethylation and transsulphuration reactions. Methionine is converted to S-adenosyl- methionine via S-adenosyl-methionine transferase. S-adenosyl- methionine further forms S-adenosyl- homocysteine via transmethylation reaction and is subsequently converted into homocysteine via adenosylhomocysteinase. Homocysteine in the presence of serine and cystathionine-β-synthase forms cystathione which finally forms cysteine via cystathione-γ-lyase or cystathionase. This set of reactions from homocysteine to cysteine constitutes the transsulphuration reactions. All organisms contain transsulphuration enzymes, however the transsulphuration pathways can have different variations. A comparison of the transsulphuration pathways of the yeast *S.cerevisiae*, mammals, and *E.coli* is shown in Figure 2.

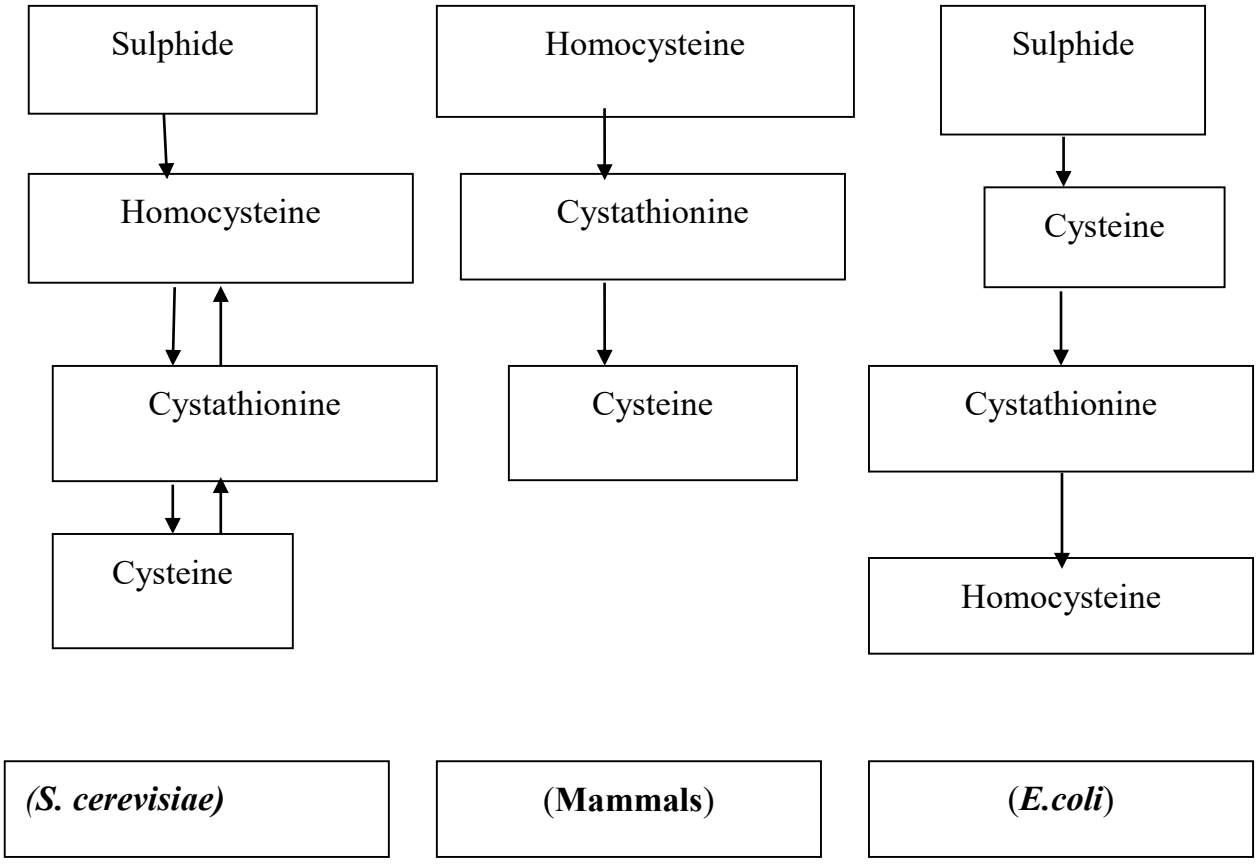

Figure 2. Transsulphuration pathways in different organisms

2. CONCLUSION

Sulphur is the key player in the catalytic functions of the biomolecules in all the living cells. It is incorporated into amino acids as cysteine and methionine, which are used to build proteins and other important molecules. The Sulphur assimilatory pathways of eukaryotic organisms that have been extensively investigated experimentally include the well-studied *Saccharomyces cerevisiae*, and alternative pathways in the plant *Arabidopsis thaliana* and humans. Plants also reduce sulphate but by a different pathway while mammals lack this ability and thus assimilate reduced sulfur (such as methionine) directly. In animals, sulfur assimilation occurs primarily through diet, as animals cannot produce sulfur-containing compounds directly. Big Data experiments have significantly resulted in a better understanding of sulfur metabolism. The Systems biology approach together with transcriptome and metabolome research will help to delineate the mechanism and regulatory aspects of Sulphur metabolism.

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CONFLICT OF INTEREST

We have no conflict of interest.

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