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Molybdenum cofactor and human disease

Guenter Schwarz

Four molybdenum-dependent enzymes are known in humans, each harboring a pterin-based molybdenum cofactor (Moco) in the active site. They catalyze redox reactions using water as oxygen acceptor or donator. Moco is synthesized by a conserved biosynthetic pathway. Moco deficiency results in a severe inborn error of metabolism causing often early childhood death. Disease-causing symptoms mainly go back to the lack of sulfite oxidase (SO) activity, an enzyme in cysteine catabolism. Besides their name-giving functions, Mo-enzymes have been recognized to catalyze novel reactions, including the reduction of nitrite to nitric oxide. In this review we cover the biosynthesis of Moco, key features of Moco-enzymes and focus on their deficiency. Underlying disease mechanisms as well as treatment options will be discussed.

Address
Institute of Biochemistry, Department of Chemistry and Center for Molecular Medicine Cologne and Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Zuelpicher Str. 47, 50674 Koeln, Germany

Corresponding author: Schwarz, Guenter (gschwarz@uni-koeln.de)

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Introduction

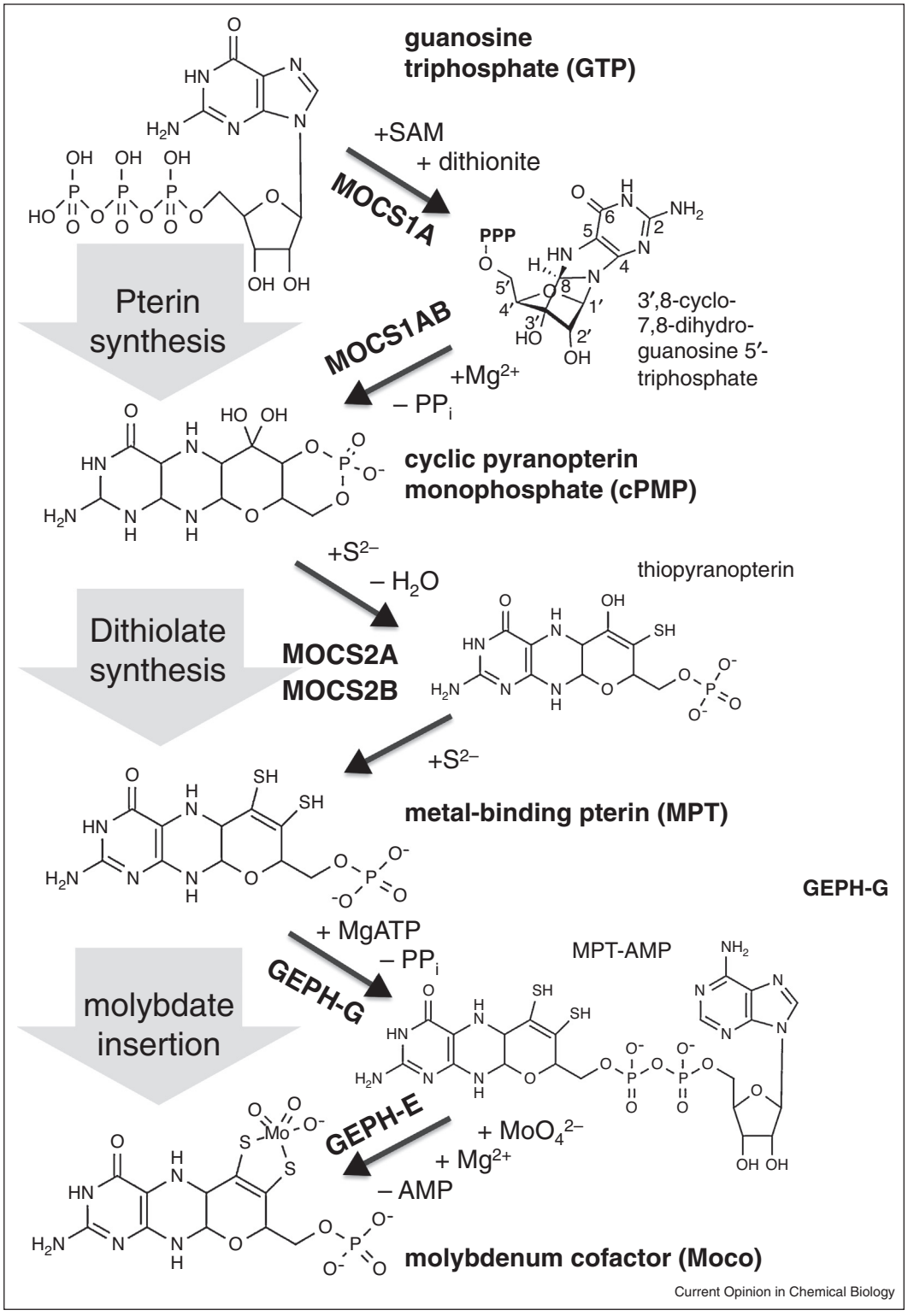
Molybdenum (Mo) is the only trace metal of the second row of the periodic table that exhibits biological activity when it is ligated to a cofactor. In nature two principal concepts of Mo cofactors have evolved, one is the iron Mo cofactor in bacterial nitrogenase and the other is represented by a large family of enzymes with more than 100 representatives relying on the pterin-based Mo cofactor (Moco) [1]. Moco-containing enzymes catalyze key redox reactions in the global carbon, sulfur and nitrogen cycles [2•]. The overall reaction is characterized by the transfer of an oxygen atom to or from a substrate in a two-electron transfer reaction [2•]. Moco consists of a Mo atom covalently bound via the dithiolate moiety of a fully reduced pterin backbone with a pterin C6-substituted four-carbon side chain forming a third pyran ring, commonly referred to as molybdopterin (MPT) or metal binding pterin [3] (Figure 1). Moco is found in all kingdoms of life, with most representatives in Prokarya that chelate Mo by either one or two MPT moieties harboring additional modification by guanine or cytosine [4]. In the following, we focus on the function of Moco in men; however, many aspects can be generalized to eukaryotic Moco synthesis.

Molybdenum cofactor biosynthesis

In all kingdoms of life, Moco is synthesized by a conserved biosynthetic pathway that can be divided into four steps [3], according to the biosynthetic intermediates cyclic pyranopterin monophosphate (cPMP), MPT and adenylated MPT (MPT-AMP) (Figure 1). Moco biosynthesis starts with the conversion of GTP into cPMP in a complex rearrangement reaction catalyzed in humans by two proteins, MOCS1A and MOCS1AB. Both proteins are expressed from the *MOCS1* gene encoding a variety of alternatively spliced transcripts [5] of which one variant (type I) expresses the MOCS1A protein encoded by exons 1–9. The transcript also contains a second open reading frame encoded by exon 10 [5]. Other variants (type II and III) represent transcripts that are derived from a truncation or deletion of exon 9 causing a loss of the first stop codon and a continuous open reading frame encoded by exon 1–10, representing the MOCS1AB protein with an additional MOCS1B domain [5]. MOCS1A binds two [4Fe-4S] clusters and belongs to the family of radical S-adenosylmethionine-dependent enzymes of the glycyl radical type [6]. The bacterial orthologues of MOCS1A and the MOCS1B domain, MoaA and MoaC, respectively, have been studied intensively leading to the discovery of their structure, reaction mechanisms, and unique reaction intermediates [7,8]. Recently, the complex reaction converting GTP into cPMP has been dissected thus demonstrating that the radical SAM protein MoaA converts GTP into 3′,8-cyclo-7,8-dihydro-GTP (Figure 1) and that this reaction is dependent on the C-terminal double glycine motif of MoaA and MOCS1A providing an essential mechanism to trigger the free radical reaction [9]. Subsequently, 3′,8-cyclo-7,8-dihydro-GTP undergoes major rearrangement reaction at the MoaC protein to yield cPMP with the pyran ring, a germinal diol and cyclic phosphate [10••,11]. The chemical structure of the first stable intermediate in Moco biosynthesis, cPMP (Figure 1), has been clarified by ^{13}C NMR studies [12]. Chemical synthesis of cPMP has been achieved recently, representing the first synthetic route for a biologically active derivative of Moco [13••].

In the second step of Moco biosynthesis, two sulfur atoms are transferred to cPMP to form the MPT dithiolate. The reaction is catalyzed by the enzyme MPT-synthase, a

Figure 1



Biosynthesis of the molybdenum cofactor. Major and transient intermediates of the three steps are shown. Cosubstrates for each reaction step are depicted at the arrows.