# Structural Investigation of Substrate Binding in Mevalonate Kinase

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## Abstract

Mevalonate kinase (MK) is an enzyme of the mevalonate pathway, which is responsible for isoprenoid precursor production. MK phosphorylates mevalonate using ATP to produce mevalonate-5-phosphate (Fig. 1).


Figure 1: The MK-catalyzed reaction.[1]

MK is a key enzyme of the mevalonate pathway, as it is the target of feedback inhibition, which makes it an important enzyme to study in pathway. [2-5]

## Background

The mevalonate pathway is an important pathway that exists in both eukaryotes and in many microorganisms. The products of the mevalonate pathway are activated isoprene units that are used as synthetic precursors for many biomolecules, such as steroids and isoprenoids.

MK is found in eukaryotes and in some bacteria and archaea. Many recent studies have focused on mammalian[2] and protozoan trypanosome MKs such as *Leishmania major* and *Trypanosoma evansi*.[4]

The study of MK structure is significant, as MK deficiency is implicated in inherited human diseases like mevalonic aciduria and hyperimmunoglobulinemia D/periodic fever syndrome (HIDS).[2] In addition, the study of trypanosomal MK is also important, as the protozoan trypanosomatid class of parasites is related to high occurrence rate of disease in human and livestock. For example, *Trypanosoma brucei* infection is responsible for sleeping sickness in Africa, *Trypanosoma cruzi* is responsible for Chagas disease in South and Central America, and the *Leishmania* genus is responsible for cutaneous, mucocutaneous and visceral forms of disease in tropical and subtropical areas.[4] Finally, the study of MK structure is important to understand the regulation of the mevalonate pathway, as the enzyme represents an important metabolic control point in many organisms.

## Overall and ATP-Bound MK Structure

The structure of MK from *Rattus norvegicus* (RnMK) in complex with MgATP reveals a high degree of structural similarity with the GHMP kinases, such as homoserine kinase (HSK). However, noticeable contrasts include a difference in N-terminal domain conformation (Fig. 2), as well as an *anti* conformation of the bound ATP nucleotide in RnMK compared to the *syn* conformation observed in HSK.[2]

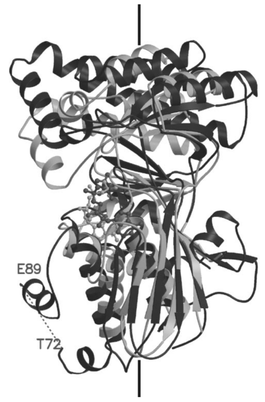


Figure 2: Overlay of ATP-bound structures of RnMK (dark gray) and HSK from *Methanocaldococcus jannaschii (*light gray).[2]

The sequences of RnMK and human MK (hMK) are 81.8% identical.[2] Although no structure of ATP-bound hMK has been determined, it would be reasonable to infer that the ATP-binding sites of RnMK and hMK are similar (Fig. 3).

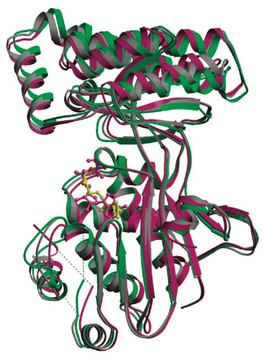

Figure 3: Structures of RnMK-FSP complex (gray), RnMK-ATP complex (magenta), and apo hMK (green). Dotted lines indicate disordered regions. FSP and ATP are shown in ball-and-stick in element colors (C in yellow) and magenta, respectively.[3]

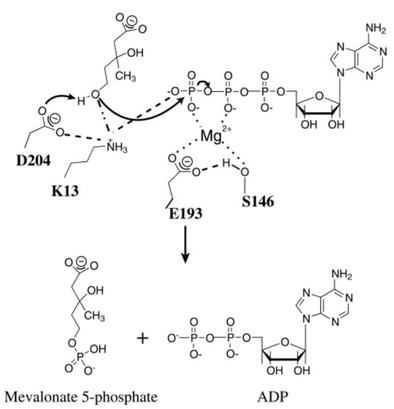


Figure 4: Proposed MK mechanism (RnMK residue numbering) based on the structure in Fig. 3 and previous mutagenesis studies.[2]

## Additional Insights

While the structures of some MKs have been studied, many structural details remain a mystery. For trypanosomal MK, only homology models are available (Fig. 5). The ternany complex depicting ATP and mevalonate binding has also not been determined.

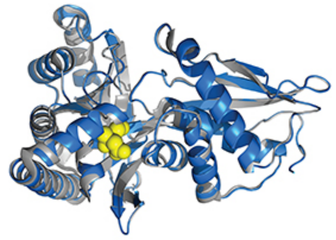

Figure 5: Homology model of MK from *T. evansi* (blue) and structure of MK from *L. major* (gray), with the expected binding site for mevalonate (yellow) shown in the active site.[5]

The structures of an ATP-binding lobe differs widely between MK homologs (Fig. 6), but structures of these MKs bound to ATP are unknown. Solving these structure will give us insight into differences in ATP- and inhibitor-binding among homologs.[1]

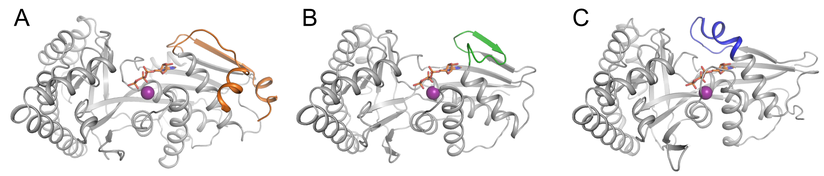


Figure 6: Structures of (A) RnMK, (B) MK from *Methanosarcina mazei*, and (C) MK from L. major (LmMK) in gray, with ATP-binding lobe in orange, green, and blue, respectively. ATP (sticks) and $Mg^{2+}$ (sphere) are modeled from the ATP-bound RnMK structure.

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