

## 1 Nomenclature

### EC number

4.99.1.8

### Systematic name

Fe<sup>3+</sup>:ferritroporphyrin IX ligase ( $\beta$ -hematin-forming)

### Recommended name

heme ligase

### Synonyms

HDP <1,2> [1,2]

heme detoxification protein <1,2> [1,2]

## 2 Source Organism

<1> *Plasmodium falciparum* [1,2,3]

<2> *Plasmodium yoelii* [2]

## 3 Reaction and Specificity

### Catalyzed reaction

2 ferritroporphyrin IX =  $\beta$ -hematin

### Natural substrates and products

**S** ferritroporphyrin IX <1> (<1> hemozoin consists of an unusual polymer of hemes linked between the central ferric ion of one heme and a carboxylate side-group oxygen of another. The hemes are sequestered via this linkage into an insoluble product, providing a unique way for the malaria parasite to avoid the toxicity associated with soluble heme [3]) (Reversibility: ?) [3]

**P**  $\beta$ -hematin

### Substrates and products

**S** ferritroporphyrin IX <1,2> (<1> hemozoin consists of an unusual polymer of hemes linked between the central ferric ion of one heme and a carboxylate side-group oxygen of another. The hemes are sequestered via this linkage into an insoluble product, providing a unique way for the malaria parasite to avoid the toxicity associated with soluble heme [3]; <2> HDP possesses 2.7 heme binding sites [2]; <1> hemozoin con-

sists of an unusual polymer of hemes linked between the central ferric ion of one heme and a carboxylate side-group oxygen of another [3]) (Reversibility: ?) [2,3]

**P**  $\beta$ -hematin

**pH-Optimum**

3-4.4 <1> [2]

**pH-Range**

3.3-5.2 <1> (<1> pH 3.3-4.4: optimum, pH 5.2: about 75% of maximal activity, no activity above pH 5.6 [2]) [2]

## 5 Isolation/Preparation/Mutation/Application

**Localization**

extracellular <1> (<1> the parasite utilizes a circuitous outbound-inbound trafficking route by initially secreting HDP into the cytosol of infected red blood cells [2]) [2]

food vacuole <1> [2]

**Purification**

<1> (native enzyme, full-length recombinant enzyme and truncated enzymes) [2]

<2> (recombinant enzyme) [2]

**Cloning**

<1> (expression of full length enzyme in *Escherichia coli*, expression of two truncated enzyme proteins (HDP3 encoded by amino acids 88-205 of the full-length protein, representing the fasciclin domain and HDP2 encoded by amino acids 1-87 and lacking the fasciclin domain)) [2]

<2> (expression in *Escherichia coli*) [2]

**Engineering**

Additional information <1> (<1> the truncated enzyme proteins HDP3 (encoded by amino acids 88-205 of the full-length protein, representing the fasciclin domain) and HDP2 (encoded by amino acids 1-87 and lacking the fasciclin domain) are unable to produce hemozoin. The full-length enzyme is required for heme binding and hemozoin production activities of the protein [2]) [2]

**Application**

medicine <1,2> (<1> HDP is a conserved target for future antimalarial development [1]; <1,2> involvement of heme detoxification protein in the process of formation of hemozoin suggests that it could be a malaria drug target [2]) [1,2]

## 6 Stability

### Temperature stability

94 <1> (<1> 10 min, stable [2]) [2]

## References

- [1] Vinayak, S.; Rathore, D.; Kariuki, S.; Slutsker, L.; Shi, Y.P.; Villegas, L.; Escalante, A.A.; Udhayakumar, V.: Limited genetic variation in the *Plasmodium falciparum* heme detoxification protein (HDP). *Infect. Genet. Evol.*, **9**, 286-289 (2009)
- [2] Jani, D.; Nagakatti, R.; Beatty, W.; Angel, R.; Slebodnick, C.; Andersen, J.; Kumar, S.; Rathore, D.: HDP - a novel heme detoxification protein from the malaria parasite. *PLoS Pathog.*, **25**, 0000 (2008)
- [3] Slater, A.F.G.; Swiggard, W.J.; Orton, B.R.; Flitter, W.D.; Goldberg, D.E.; Cerami, A.; Henderson, G.B.: An iron-carboxylate bond links the heme units of malaria pigment. *Proc. Natl. Acad. Sci. USA*, **88**, 325-329 (1991)