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Comprehensive structural analysis of the open and closed conformations of *Theileria annulata* enolase by molecular modelling and docking

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ABSTRACT

Theileria annulata is an apicomplexan parasite which is responsible for tropical theileriosis in cattle. Due to resistance of *T. annulata* against commonly used antitheilerial drug, new drug candidates should be identified urgently. Enolase might be a druggable protein candidate which has an important role in glycolysis, and could also be related to several cellular functions as a moonlight protein. In this study; we have described three-dimensional models of open and closed conformations of *T. annulata* enolase by homology modeling method for the first time with the comprehensive domain, active site and docking analyses. Our results show that the enolase has similar folding patterns within enolase superfamily with conserved catalytic loops and active site residues. We have described specific insertions, possible plasminogen binding sites, electrostatic potential surfaces and positively charged pockets as druggable regions in *T. annulata* enolase.

1. Introduction

Enolase is mainly responsible for catalyzing the interconversion of 2-phosphoglycerate (2-PGA) and phosphoenol pyruvate (PEP) in glycolytic pathway. The enzyme has also several pathogenic features such as plasminogen and fibronectin binding activities (Avilán et al., 2011; Bao et al., 2014; Toledo et al., 2012). Despite the non-glycolytic functions of enolase has not been clarified completely yet (Paludo et al., 2015), the enzyme has sophisticated roles such as being part of protein clusters related to transcription, development, growth, aging, death, apoptosis in cells and they have been named as "moonlighting" functions (Avilán et al., 2011; Paludo et al., 2015).

Tropical theileriosis is caused by the apicomplexan parasite *Theileria annulata* which is transmitted by a tick vector from the genus *Hyalomma* in cattle (Echebli et al., 2014; Li et al., 2014). *Theileria* parasites invade the leukocytes by sporozoites secreted from the vector, schizonts mature into merozoites and infect erythrocytes subsequently; leading to high rate of morbidity and mortality (Mans et al., 2015; Razavi et al., 2011; Sharifiyazdi et al., 2012). Some recent studies reported that *T. annulata* has developed resistance to buparvaquone; a well-known drug used in the treatment of theileriosis (Marsolier et al., 2015; Mhadhbi et al., 2010; Sharifiyazdi et al., 2012). Therefore; *T. annulata* enolase could be a possible target for new drug-design studies because of emerging requirement for alternative drugs against the parasite.

Homology modeling is one of the prominent step in structure-based drug design studies and provides information to estimate 3D structure and druggable candidate sites of molecular targets in the absence of experimentally solved 3D structures (Agrawal, 2013). The modeled structures ensure information about functional and evolutionary features of the target proteins (Wallner and Elofsson, 2005). Furthermore, molecular docking is used to determine optimum binding modes of ligands to a certain site of protein target in structure-based drug design (Thomsen and Christensen, 2006). Present study has been conducted to evaluate druggable potential of *Ta*ENO for new drug design studies. The 3D open and

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