

Molecular dynamics simulations of *Plasmodium falciparum* Fe-superoxide dismutase

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Abstract: Malaria is a parasite disease caused by *Plasmodium* spp. that affects 214 million people, with more than 400,000 deaths per year [1]. Among the protozoan species, *P. falciparum* is responsible for almost severe form, cerebral malaria and deaths due to malaria. Despite of epidemiological data, drugs available for its treatment have limited efficacy and safety profile [2]. Aiming at circumvents this dilemma, key enzymes of the parasite can be targeted to identify new promisse drugs. Fe-superoxide dismutase from P. falciparum (PfFe-SOD) plays a crucial role against reactive oxygen species (ROS) that are likely formed during intraerytrocitic stage due to haemoglobin breakdown and can be lethal for parasites. Thus, this target is considered a promising target for drug development. However, it would appear difficult to inhibit PfFe-SOD using classical 'active-site directed' approaches, because the orthosteric site can acommodade just two atoms (e.g. superoxide). Thus, molecular dynamics (MD) simulations on GROMACS 5.1.2 program [3] were employed to predict potential allosteric site. The AMBER99SB-ILDN force field [4] was adapted to support Fe⁺² cations on a non-bonded model [5]. The interactions were described by a potential with Coulombic and Lennard-Jones terms obtained through various particle mesh Ewald (PME) simulations and chosen to minimize the error the experimenttal values of hydration free energy (HFE) and distance between the ion and the oxygen of the first solvation shell (ion-oxygen distante, IOD). The selected water model was single point (SPC/E) because it had the fewest error for Fe^{2+} [5]. The MD charge extended simulations (70 ns) were performed with a periodic boundary in the NPT (T = 298 K, P=1 atm). We used a time step of 2 ps and a short range interaction cuttof radius of 1.4 nm. The convergence parameters from MD (Fig. 1) suggest stability after 35 ns (RMSD = 0.16 ± 0.03 nm) with normal fluctuations from c-alpha (RMSF < 0.11 ± 0.04 nm; except for loops regions). The most representative structure was selected by the GROMOS clustering algorithm with a 0.25 nm cut-off then submitted to AlloSite 2.0 to predict allosteric sites [6]. The covariance matrix (Fig. 2; maximum: 0.0671; minium: -0.0168) suggests some correlation between a predicted site and the active one. A maximum inter-site value of 0.005 between the pairs HIS26B/TYR27B, and minimum intersite value of -0.005 between the pairs HIS161/TYR9B, HIS161A/PRO82B, HIS26A/PRO82B and HIS26A/CYS84B. This possible allosteric site will be use for virtual screening campaings to indetify promise allosteric PfFe-SOD drugs against



malaria.

Figure 1: Convergence parameters from MD simulations: RMSD (C-alpha) (a) and RMSF (C-alpha) (b) of PfFe-SOD during the DM simulations. The highlighted areas in RMSD and RMSF graphics correspond to productive phase and loops regions respectively.



Figure 2: Correlation matrix reduced to show only the predicted allosteric site by the active site: the active site (vertical axis) by the predicted allosteric site (horizontal axis) correlation. The red surface on the structure represents the allosteric prediction.



Keywords: Allosteric site, malaria, molecular dynamics, superoxide dismutase.

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