Biochem Anal Biochem 2016, 5:3(Suppl)
http://dx.doi.org/10.4172/2161-1009.S1.006

Disruption of falcipains processing by blocking hotspot spot residues of domains in malaria parasite

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Falcipains are among the critical enzymes required for parasite machinery in malaria. Our previous study suggested that they have unique pro and mature domains that interact via salt bridge and hydrophobic interactions, which are essential for their activation. Designing small molecules that interfere at the hotspot residues of domains would inhibit falcipains activation. Although multiple active site inhibitors exist for falcipains, specific inhibitors that halt processing without binding to active site remains unknown. Our study suggested that azapeptide compounds based on conformationally constrained disubstituted β- and γ-amino acids inhibit the activation of falcipains. Among these, C-02 and C-07 hinders the falcipains activity by binding to intact pro-FP2 rather than mature active FP2 during hemoglobin hydrolysis and fluorogenic substrate assay. While these compounds did not affect the secondary structure of protein during circular dichroism spectroscopy, surface Plasmon resonance result demonstrated over the range of inhibitor concentration indicated specific interaction with FP3 and equilibrium constant ~80nM. Moreover, confirmation was done by MD simulations for ~5×130 ns confirms that compound-inhibitor complex provides rigidity to the pro domain to remain intact even at low pH preventing activation of the enzyme. For further authentication inhibitory concentration (IC50), of compound were examined on 3D7 strain of *Plasmodium falciparum*, parasite shows distorted trophozoite morphology with IC50 ~250 nM. Further, we reported a conserved histidine residue (His205) in pro domain of FP3, essential for pH sensing during auto-processing. Collectively, we provide a framework for targeting hotspot residues that can regulate falcipains in zymogen condition and halts its activation.

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Association between single nucleotide polymorphism +874 A/T and its susceptibility to pediatric tuberculosis in Indonesia

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Tuberculosis (TB) is one of the leading causes of morbidity and mortality worldwide especially, in developing countries. TB is a complex multifactorial disease with genetic as one of the substantial factors for TB development. Our hypothesis is that single nucleotide polymorphism (SNP) +874 A/T affects low production of IFN-γ level that increased susceptibility of pediatric TB. The aim of this study was to investigate association between SNP +874 A/T and its susceptibility to pediatric TB in Indonesia. DNA samples were obtained from 50 patients with pulmonary TB, 1 patient with extra pulmonary TB and 51 healthy controls. SNP +874 A/T was identified using the amplification refractory mutational system polymerase chain reaction (ARMS-PCR) method. The result of this study showed the presence of AA, AT and TT genotype in TB patients were 31 (60.8%), 20 (39.2%) and 0 (0%); respectively (p=0.023). Significant decreased in production of IFN-γ level (p=0.042) was found in TB patients (10.49±6.26 pg/ml) which contrast to healthy controls (10.80±14.48 pg/ml). Low production of IFN-γ level was identified among AA genotype patients (10.44±8.24 pg/ml) compared to AT genotype patients (11.17±13.71 pg/ml), but not significantly proven. An allele was found to be a risk factor for development of TB disease (OR, 1.51; 95% CI=1.04-2.21, p=0.018). In conclusion, this study has provided evidence of the association between SNP +874 A/T and its susceptibility to pediatric TB. AA genotype and an allele were found significant among pediatric TB patients in Indonesia.

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