Farhana Mosaddeque 論文内容の要旨

主　論　文

Prediction Model for Antimalarial Activities of Hemozoin Inhibitors by Using Physicochemical Properties

物理化学的特性を用いたヘモゾイン阻害薬の抗マラリア活性予測モデル構築

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緒　　言

Despite significant advances in the prevention and treatment of malaria, it remains to be one of the calamitous global health and socioeconomic concern. Several drugs are currently available for malaria treatment, however parasites began to develop resistance against most of these drugs including the first line drug, Artemisinin. A newly approved vaccine, *RTS, S*, has raised hope for preventive therapy, yet suffered with limited efficacy (shorter and stage-specific immunity). As a result, look for new small molecule drug candidates with novel target/mechanism of action has become pivotal. There are various phenotypic screening methods to identify novel antimalarials, however, most of them are time-consuming, costly and laborious. In contrary, *in silico* approach found to be effective to screen millions of compounds comparatively at shorter time and less expensive way than conventional screening. Therefore, in this study, we developed new prediction models for *in silico* antimalarial compound screening based on the physicochemical properties of small chemical compounds (hemozoin inhibitors) identified from our previous study.

対象と方法

In this study, 224 positive hemozoin inhibitors (obtained from our previous study), were tested for *in vitro* erythrocytic antimalarial activity against chloroquine - mefloquine sensitive *Plasmodium falciparum* strain, 3D7A and their antihemozoin activity. The physicochemical properties of the active compounds (antimalarials and hemozoin inhibitors) were extracted from ChemSpider and SciFinder databases. To develop the model, univariable logistic regression was performed to examine the association between physicochemical properties (variables) and antimalarial activity of the compounds (outcome). Subsequently, to find independent predictors, variables $P<0.1$ and/or significant variables in previous study, were subjected to multivariable analysis using Bayesian model averaging (BMA) based on the Bayesian information criterion (BIC), where the smaller BIC value indicates the better model. The data were randomly divided into two sets - training and testing, with a ratio of 70:30. The BMA models were developed using training set and validated by testing data set. The data were analysed by using RStudio 1.0.44

and P<0.05 were considered statistically significant.

結　　果

The BMA analysis identified 37 models, among which 5 best models were chosen. The BMA model with a cut-off of 0.09, revealed the sensitivity, specificity and accuracy of 60%, 69.23% and 91.23%, respectively. According to our prediction models, the best predictors (physicochemical properties) that significantly associated with antimalarial activity among compounds possessing hemozoin inhibition activity were - lower number of S atoms, lower Log D values at pH 3, 4 and 5, and higher ACD Log D value at pH 7.4.

考　　察

It was previously reported that replacement of the ring oxygen by sulfur (S toms) results in decreased antihemozoin and antimalarial activity. Additionally, LogD - value at pH 3, 4 and 5 and ACD LogD - value at pH 7.4, are related to the compound's lipophilicity (entrance) and trapping (accumulation) inside the food vacuole. Thus the combination of these properties, might facilitate the identification of potential antimalarials from hemozoin inhibitors. Our prediction (BMA) model based on the physicochemical properties - is simple and convenient compared to other *in silico* screening models. The structure and ligand based *in silico* models require known structures/targets/ligands/binding site information for the analysis whereas this model can directly elucidate specific predictor(s)
(physicochemical properties) for antimalarials. Further studies by combining antihemozoin predictors (from our previous study) with antimalarial predictors as well as use of larger sample size or new compound library - are necessary to validate the model. In conclusion, prediction models for antimalarials were generated by using physicochemical properties where the best model showed higher hit rate, 17% compared to 9.8% hit rate obtained from the *in vitro* experiment.