

MOLECULAR BIOLOGY

[Malaria: from genetic and molecular biology to disease control].

1. Abstract

The knowledge of the genomic structure of *Plasmodium falciparum* and of its main vector, *Anopheles gambiae*, may offer new perspectives for malaria therapy, vaccines or control of mosquito-borne transmission. New targets for future antimalarial drugs were identified, mainly apicoplast (a vestige of a vegetal structure incorporated by the parasite) and several enzymes, particularly proteases. The practical difficulty is now to select a few number of these "promising molecules", probably no more than 3 or 4, for a preclinical and clinical pharmaceutical development. Indeed, several other antimalarial drugs are already under development, and the industrial possibilities for developing new drugs are evidently limited. Many new vaccination targets and antigenic proteins were also identified. According to scientific and industrial limitations, a complete evaluation of these antigens is absolutely necessary to select a few of them for clinical development. For anti-malarial vaccinations, DNA vaccines may offer the most interesting perspectives, with the possibility of simultaneous immunisation against different *Plasmodium* stages and of an adjuvant effect by adding a gene encoding certain cytokines. In *Anopheles gambiae* genome, several genes encoding key-proteins (particularly odorant receptors necessary for blood feeding) were identified, as other genes encoding for proteins limiting the sexual development of *Plasmodium* inside its vector. From a theoretical viewpoint, genetically modified non biting or non transmitting mosquitoes offer new perspectives for the control of malaria transmission, but until now, the preliminary practical attempts gave rather poor results. On the whole, the genomic and proteomic of *Plasmodium falciparum* and *Anopheles gambiae* yielded exciting scientific results, but it is still too early and very speculative to imagine their practical applications for the control of malaria.

<https://www.ncbi.nlm.nih.gov>

ZOOLOGY

Modelling the relative abundance of the primary African vectors of malaria before and after the implementation of indoor, insecticide-based vector control.

[Sinka ME](#)¹, [Golding N](#)², [Massey NC](#)³, [Wiebe A](#)⁴, [Huang Z](#)⁵, [Hay SI](#)^{6,7,8}, [Moyes CL](#)⁹.

Author information

2. Abstract

BACKGROUND:

Malaria remains a heavy burden across sub-Saharan Africa where transmission is maintained by some of the world's most efficient vectors. Indoor insecticide-based control measures have significantly reduced transmission, yet elimination remains a distant target. Knowing the relative abundance of the primary vector species can provide transmission models with much needed information to guide targeted control measures. Moreover, understanding how existing interventions are impacting on these relative abundances highlights where alternative control (e.g., larval source management) is needed.

METHODS:

Using the habitat suitability probabilities generated by predictive species distribution models combined with data collated from the literature, a multinomial generalized additive model was applied to produce relative abundance estimates for *Anopheles arabiensis*, *Anopheles funestus* and *Anopheles gambiae/Anopheles coluzzii*. Using pre- and post-intervention abundance data, estimates of the effect of indoor insecticide-based interventions on these relative abundances were made and are illustrated in post-intervention maps.

<https://www.ncbi.nlm.nih.gov/pubmed/26945997>

BOTANY

Ethno-botanical survey of plants used in the traditional treatment of malaria in Sei Kepayang, Asahan of North Sumatera.

3. Abstract

To investigate and collect information from traditional health healer/tribal communities on the use of medicinal plants for treatment of malaria in Sei Kepayang, Asahan District of North Sumatera. The

ethno-botanical study was conducted in Sei Kepayang, Asahan District of North Sumatera in January-March 2013 through questionnaire and personal interviews, and their responses were documented. The present study enumerated 16 ethno-medicinal plant species belonging to 13 families used by the tribal communities and medicinal healers in Sei Kepayang, Asahan District of North Sumatera in treatment of malaria. Some of the recipes, methods of preparation and administration were also documented. From the interviews conducted, 16 plant species belonging to 13 families have been identified in the treatment of malaria.

<http://europepmc.org/abstract/med/25312101>

MICROBIOLOGY

Using infections to fight infections: paratransgenic fungi can block malaria transmission in mosquitoes.

[Rasgon JL](#)¹.

Author information

4. Abstract

EVALUATION OF: Fang W, Vega-Rodríguez J, Ghosh AK et al. Development of transgenic fungi that kill human malaria parasites in mosquitoes. *Science* 331(6020), 1074-1077 (2011).

Paratransgenesis is the genetic manipulation of insect endosymbiotic microorganisms such as bacteria, viruses or fungi. Paratransgenesis has been proposed as a potential method to control vector-borne diseases such as malaria. In this article, Fang and colleagues have used genetic manipulation to insert multiple antimalaria effector genes into the entomopathogenic fungus *Metarhizium anisopliae*. When the modified fungus was used to infect *Anopheles* mosquitoes, it expressed the antimalaria effector molecules in the mosquito hemolymph. When several different effector molecules were coexpressed, malaria levels in the mosquito salivary glands were inhibited by up to 98% compared with controls. Significant inhibition could be initiated by as little as seven fungal spores and was very rapid and long lasting. These data suggest that recombinant entomopathogenic fungi could be deployed as part of a strategy to control malaria.

<https://www.ncbi.nlm.nih.gov/pubmed/21861618>

Cultural and genetic adaptations to malaria: Problems of comparison

ANTHROPOLOGY

5. Abstract

The concept of adaptation has been used differently in studies of biological and cultural evolution, and this divergence raises the question of whether genetic and cultural adaptations are truly comparable. This paper compares genetic and cultural traits associated with endemic malaria in Sardinia, Italy. Thalassaemia and G-6-Pd deficiency, two genetic traits of the Island's population, are believed to enhance fitness against malaria, despite increased risk for the diseases of thalassaemia major and favism. Two cultural traits, a pastoral pattern of inverse transhumance and rules limiting the geographical mobility of lowland women, limited exposure to the malaria vector, *Anopheles labranchiae*; these are used as examples of cultural adaptations. The distribution, costs, and benefits of the adaptive cultural and genetic traits are compared, and the theoretical difficulties of finding a common measure of adaptive value are discussed.

<https://link.springer.com/article/10.1007/BF00889033>

ANTHROPOGENETICS

COMPARATIVE STUDY OF THE HISTORY OF SETTLEMENT OF MIKEA, A GROUP OF HUNTERGATHERERS IN MADAGASCAR THROUGH UNIPARENTAL VERSUS BIPARENTAL GENETIC

6. MARKERS

Harilanto Razafindrazaka, Denis Pierron, Francois-Xavier Ricaut & Thierry Letellier

The island of Madagascar lies in the western region of the Indian Ocean, 300 miles from the East African coast. The

island also, however, sits at the western edge of population expansions out of Island South East Asia. The origin of these populations, and the timing of their arrival in Madagascar, are still debated questions. To address this intriguing history, we have chosen to study, from an anthropogenetic approach, the Mikea, a hunter gatherer population located in the south-west region of Madagascar. Genetic elements of the population were studied using several markers including uni-parental marker Y and mtDNA chromosomes or recently bi-parental markers. Here we present a comparison between these different sets of markers and show how differences between them can provide important insights for understanding the history of this population. Furthermore, this comparison brings to

68 light advances in the understanding of the settlement history of populations in the south of the island.

<http://www.sealingproject.com>

MEDICAL GENETICS

7. Abstract

Given the importance of Africa to studies of human origins and disease susceptibility, detailed characterization of African genetic diversity is needed. The African Genome Variation Project provides a resource with which to design, implement and interpret genomic studies in sub-Saharan Africa and worldwide. The African Genome Variation Project represents dense genotypes from 1,481 individuals and whole-genome sequences from 320 individuals across sub-Saharan Africa. Using this resource, we find novel evidence of complex, regionally distinct hunter-gatherer and Eurasian admixture across sub-Saharan Africa. We identify new loci under selection, including loci related to malaria susceptibility and hypertension. We show that modern imputation panels (sets of reference genotypes from which unobserved or missing genotypes in study sets can be inferred) can identify association signals at highly differentiated loci across populations in sub-Saharan Africa. Using whole-genome sequencing, we demonstrate further improvements in imputation accuracy, strengthening the case for large-scale sequencing efforts of diverse African haplotypes. Finally, we present an efficient genotype array design capturing common genetic variation in Africa.

<http://europepmc.org/abstract/MED/25470054>

MATHEMATICAL BIOLOGY

Determining Important Parameters in the Spread of Malaria Through the Sensitivity Analysis of a Mathematical Model

8. Abstract

We perform sensitivity analyses on a mathematical model of malaria transmission to determine the relative importance of model parameters to disease transmission and prevalence. We compile two sets of baseline parameter values: one for areas of high transmission and one for low transmission. We compute sensitivity indices of the reproductive number (which measures initial disease transmission) and the endemic equilibrium point (which measures disease prevalence) to the parameters at the baseline values. We find that in areas of low transmission, the reproductive number and the equilibrium proportion of infectious humans are most sensitive to the mosquito biting rate. In areas of high transmission, the reproductive number is again most sensitive to the mosquito biting rate, but the equilibrium proportion of infectious humans is most sensitive to the human recovery rate. This suggests strategies that target the mosquito biting rate (such as the use of insecticide-treated bed nets and indoor residual spraying) and those that target the human recovery rate (such as the prompt diagnosis and treatment of infectious individuals) can be successful in controlling malaria.

<https://link.springer.com/article/10.1007%2Fs11538-008-9299-0>

EVOLUTIONARY BIOLOGY

Malaria infection and human evolution.

9. Abstract

During the evolution of the genus *Homo*, with regard to the species *habilis*, *erectus* and *sapiens*, malaria has played a key biological role in influencing human development. The plasmodia causing malaria have evolved in two ways, in biological and phylogenetic terms: *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale* appear to have either coevolved with human mankind, or encountered human species during the most ancient phases of *Homo* evolution; on the other hand, *Plasmodium falciparum* has been transmitted to humans by monkeys in a more recent period, probably between the end of the Mesolithic and the beginning of the Neolithic age. The authors show both direct and indirect biomolecular evidence of malarial infection, detected in buried subjects, dating to ancient times and brought to light in the course of archaeological excavations in major Mediterranean sites. In this review of the literature the authors present scientific evidence confirming the role of malaria in affecting the evolution of populations in Mediterranean countries. The people living in several different Mediterranean regions, the cradle of western civilization, have been progressively influenced by malaria in the course of the spread of this endemic disease in recent millennia. In addition, populations affected by endemic malaria progressively developed cultural, dietary and behavioural adaptation mechanisms, which contributed to diminish the risk of disease. These habits were probably not fully conscious. Nevertheless it may be thought that both these customs and biological modifications, caused by malarial plasmodia, favoured the emergence of groups of people with greater resistance to malaria. All these factors have diminished the unfavourable demographic impact of the disease, also positively influencing the general development and growth of civilization.

<http://europepmc.org/abstract/med/20424529>

ECOLOGY

10. Abstract

Background

Standard advice regarding vector control is to prefer interventions that reduce the lifespan of adult mosquitoes. The basis for this advice is a decades-old sensitivity analysis of ‘vectorial capacity’, a concept relevant for most malaria transmission models and based solely on adult mosquito population dynamics. Recent advances in micro-simulation models offer an opportunity to expand the theory of vectorial capacity to include both adult and juvenile mosquito stages in the model.

Methods

In this study we revisit arguments about transmission and its sensitivity to mosquito bionomic parameters using an elasticity analysis of developed formulations of vectorial capacity.

<https://academic.oup.com/inthealth/article/7/2/121/663241/Adult-vector-control-mosquito-ecology-and-malaria>

CHEMISTRY

Parasite killing in *Plasmodium vivax* malaria by nitric oxide: implication of aspartic protease inhibition.

[Sharma A¹](#), [Eapen A](#), [Subbarao SK](#).

[Author information](#)

11. Abstract

Nitric oxide (NO) is known to possess antiparasitic activity towards *Plasmodium* species. Parasite proteases are currently considered to be promising targets for antimalarial chemotherapy. In the present study, we have studied the inhibitory effect of NO on the activity of plasmepsin in *Plasmodium vivax*, the pepsin-like aspartic protease which is believed to be involved in the cleavage during hemoglobin degradation in *Plasmodium falciparum*. NO donors (+/-) (E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide (NOR-3), S-nitrosoglutathione (GSNO), and sodium nitroprusside (SNP) were found to inhibit this plasmepsin activity in a dose-dependent manner in purified *P. vivax* aspartic protease enzyme extracts. This inhibitory effect may be attributable to the nitrosylation of the cysteine residue at the catalytic site. However, an inhibitor of aspartic protease activity, namely pepstatin, was also found to inhibit (IC₅₀ 3 µM) the enzyme activity, which we have used as a positive control. Our results therefore provide novel insights into the pathophysiological mechanisms, and will be useful for designing strategies for selectively

upregulating NO production in *P. vivax* infections for antimalarial chemotherapy and also biochemical adaptations of the malaria parasite for survival in the host erythrocytes with a better understanding of the protease substrate interactions.

<https://www.ncbi.nlm.nih.gov/pubmed/15598889>

DIAGNOSTICS

Malaria Diagnostics in Clinical Trials

12. Abstract

BACKGROUND:

The need for new malaria surveillance tools and strategies is critical, given improved global malaria control and regional elimination efforts. High quality *Plasmodium falciparum* DNA can reliably be extracted from malaria rapid diagnostic tests (RDTs). Together with highly sensitive molecular assays, wide scale collection of used RDTs may serve as a modern tool for improved malaria case detection and drug resistance surveillance.

However, comparative studies of DNA extraction efficiency from RDTs and the field applicability are lacking. The aim of this study was to compare and evaluate different methods of DNA extraction from RDTs and to test the field applicability for the purpose of molecular epidemiological investigations.

METHODS:

DNA was extracted from two RDT devices (Paracheck-Pf® and SD Bioline Malaria Pf/Pan®), seeded in vitro with 10-fold dilutions of cultured 3D7 *P. falciparum* parasites diluted in malaria negative whole blood. The level of *P. falciparum* detection was determined for each extraction method and RDT device with multiple nested-PCR and real-time PCR assays. The field applicability was tested on 855 paired RDT (Paracheck-Pf) and filter paper (Whatman® 3MM) blood samples (734 RDT negative and 121 RDT positive samples) collected from febrile patients in Zanzibar 2010. RDT positive samples were genotyped at four key single nucleotide polymorphisms (SNPs) in *pfmdr1* and *pfert* as well as for *pfmdr1* copy number, all associated with anti-malarial drug resistance.

<https://www.ncbi.nlm.nih.gov/pubmed/23510231>