42

Turning a vulnerability into a strength - deciphering the protective mechanisms of pyruvate kinase deficiency against malaria

Ana Balau[1], Daniel Sobral[4], Márcia Medeiros[2], Sandra Antunes[1], Maria Carvalho[2], Inês Morais[1], Filomena Carvalho[3], João Paulo Gomes[4], Alexandra M M Antunes[5], Ana Paula Arez[1]

1 Global Health and Tropical Medicine, GHTM IHMT NOVA, Portugal
2 Institute of Hygiene and Tropical Medicine (IHMT), Portugal
3 Instituto de Medicina Molecular João Lobo Antunes, Portugal
4 Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal
5 University of Lisbon, Portugal

Presenter: Ana Paula Arez

Malaria remains a global health challenge and despite the considerable progress made in the mortality rate, the 2025 target of the Global Technical Strategy 2016–2030 is still far from being reached. New strategies to improve patient management, prevent severe cases, and reduce deaths, are urgently needed.
Exploring interactions between the malaria parasite and host red blood cells (RBCs) offers opportunities to find these novel tools. Pyruvate kinase deficiency (PKD) has been associated with malaria resistance. The elevated concentration of the specific mammalian metabolite 2,3-diphosphoglycerate (2,3-DPG), associated with PKD, may hinder glycolysis, and prompted us to hypothesise its potential contribution to PKD-mediated protection.
We investigated the impact of the extracellular supplementation of 2,3-DPG on the Plasmodium falciparum intraerythrocytic developmental cycle in vitro. Results showed a hindrance of parasite growth, likely attributed to the production of significantly less progeny from 2,3-DPG-treated parasites. Untargeted metabolomic analysis revealed that the metabolic profile of treated infected cells became more like that of non-infected cells. Alterations in membrane structure, cell morphology, and biomechanics have been analysed by atomic force microscopy. 2,3-DPG treatment induced mild modifications in RBC membranes compared to the profound influence exerted by the parasite on host cells. Mild modification of non-infected RBCs' height and stiffness did not impact the egress or invasion of parasite.
Differential gene expression and the transcriptomic profile of P. falciparum trophozoites were analysed using nanopore sequencing technology. 71 genes exhibited significant differential expression from the non-exposed parasites to 2,3-DPG mostly associated with the GO terms nucleic acid binding, transcription, or monoatomic anion channel. Further, several genes related to cell cycle control were downregulated in treated parasites, suggesting that the presence of this RBC-specific glycolytic metabolite impacts the expression of genes transcribed during the parasite trophozoite stage and the number of merozoites released from individual schizonts, which supports the potential role of 2,3-DPG in the mechanism of protection against malaria by PKD.