Journal of Biomechanics 44 (2011) 1553–1558

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Margination of red blood cells infected by *Plasmodium falciparum* in a microvessel

Yohsuke Imai [a,*], Keita Nakaaki [a], Hitoshi Kondo [a], Takuji Ishikawa [a], Chwee Teck Lim [b], Takami Yamaguchi [c]

[a] Department of Bioengineering and Robotics, Graduate School of Engineering, Tohoku University, 6-6-01 Aramaki Aza Aoba, Sendai 980-8579, Japan
[b] Mechanobiology Institute, Division of Bioengineering and Department of Mechanical Engineering, National University of Singapore, Singapore
[c] Department of Biomedical Engineering, Graduate School of Biomedical Engineering, Tohoku University, Japan

ARTICLE INFO

Article history:
Accepted 25 February 2011

Keywords:
Malaria
Margination
Hydrodynamic interaction
Numerical simulation

ABSTRACT

We investigated numerically the mechanism of margination of *Plasmodium falciparum* malaria-infected red blood cells (*Pf*-IRBCs) in micro-scale blood flow. Our model illustrates that continuous hydrodynamic interaction between a *Pf*-IRBC in the trophozoite stage (*Pf*-T-IRBC) and healthy red blood cells (HRBCs) results in the margination of the *Pf*-T-IRBC and, thus, a longer duration of contact with endothelial cells. The *Pf*-T-IRBC and HRBCs first form a "train". The volume fraction of RBCs is then locally increased, to approximately 40%, and this value is maintained for a long period of time due to the formation of a long train in high-hematocrit conditions. Even in low-hematocrit conditions, the local volume fraction is instantaneously elevated to 40% and the *Pf*-T-IRBC can migrate to the wall. However, the short train formed in low-hematocrit conditions does not provide continuous interaction, and the *Pf*-T-IRBC moves back to the center of the channel.

1. Introduction

Malaria continues to be one of the most serious infectious diseases. Approximately 3.3 billion people are at risk, and each year it leads to approximately 1 million deaths (World Health Organization, 2008). A malaria parasite, *Plasmodium falciparum*, invades and grows within its host's red blood cells (RBCs) (Miller et al., 2002). The parasite exports proteins that modify the cytoskeleton and membrane (Glenister et al., 2002; Mills et al., 2007). The *P. falciparum*-infected RBC (*Pf*-IRBC) then undergoes an increase in stiffness and change in shape from biconcave to more spherical. The parasite's exported proteins also mediate cytoadherence of the *Pf*-IRBC to endothelial cells (ECs). The principal ligand is *P. falciparum* erythrocyte membrane protein (PfEMP1) (Magowan et al., 1988), which interacts with a variety of endothelial receptor molecules such as CD36 (Barnwell et al., 1989; Ockenhouse et al., 1992) and intracellular adhesion molecule-1 (ICAM-1) (Berendt et al., 1989).

Pf-IRBCs in the late stages of infection, the trophozoite (*Pf*-T-IRBCs) and the schizont (*Pf*-S-IRBCs) stages, do not appear in peripheral blood. They are well known to sequester in the microvasculature. Ho et al. (2000) reported that *Pf*-IRBCs adhered in postcapillary venules and arterioles. One important outcome of this sequestration is to prevent *Pf*-IRBCs from splenic clearance; another is the occlusion of the microvasculature (Cooke et al., 2001). A *Pf*-IRBC can tether and roll on ECs, and then adhere to the ECs, mimicking the adhesion process of leukocytes to the vascular wall (Cooke and Coppell, 1995; Cooke et al., 2000; Ho et al., 2000). To establish contact with ECs, the *Pf*-IRBC must migrate towards the wall; however, RBCs undergo axial migration and generate a cell-free layer near the wall under physiological conditions. Thus, the migration of *Pf*-IRBCs to the wall is likely to result from a hydrodynamic interaction between *Pf*-IRBCs and healthy RBCs (HRBCs). A similar situation is that of the migration of leukocytes to the wall. When RBCs migrate towards the center of a capillary, leukocytes are pushed to the wall due to a hydrodynamic interaction between the RBCs and leukocytes. This phenomenon has been termed as "margination" (Goldsmith and Spain, 1984). Hou et al. (2010) recently developed a microfluidic device inspired by leukocyte margination to separate *Pf*-IRBCs from blood samples. They demonstrated efficient separation of the *Pf*-IRBCs in blood samples of 40% hematocrit (Hct), whereas they found no significant separation in 10% Hct samples. Their results indicate that interaction with HRBCs plays an important role in the margination of *Pf*-IRBCs, but they did not observe the migration process in detail. The underlying mechanism that may depend on Hct conditions remains unclear, although its elucidation may help in our understanding of the sequestration of *Pf*-IRBCs and assist in improving the design of microfluidic devices.

In experimental studies, it is difficult to capture the three-dimensional motion of RBCs, particularly in high Hct conditions. Thus, we developed a numerical model of micro-scale blood flow

* Corresponding author. Tel.: +81 22 714 8513; fax: +81 22 795 6959.
E-mail address: yimai@pfsl.mech.tohoku.ac.jp (Y. Imai).

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doi:10.1016/j.jbiomech.2011.02.084