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► **To cite this version:**

Didier Menard, Sandrine Houzé, Nicolas Papon. RIFINing Plasmodium–NK Cell Interaction. Trends in Parasitology, 2020, 36 (10), pp.802-804. 10.1016/j.pt.2020.07.017 . hal-02942836

HAL Id: hal-02942836

<https://univ-angers.hal.science/hal-02942836v1>

Submitted on 26 Sep 2022

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1 **Spotlight**

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3 **RIFINing Plasmodium-NK cell interaction**

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18 **Keywords:** Malaria, antigen variations, natural killers, immune response inhibition

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20

21 **Abstract**

22 Among many *Plasmodium* proteins involved at the erythrocytic cycle, some exposed on the erythrocyte
23 surface drive the antigenic variability. Recently, Harrison et *al.* elucidated the structural basis by which
24 RIFINs activate LILRB1 and suppress the immune cell function. This breakthrough points out an
25 additional strategy to survive into the human host.

26 Malaria still remains a major public health issue in the tropics and a potentially fatal disease caused
27 by protozoan parasites from the genus *Plasmodium*, although major progresses have been achieved in
28 the last two decades, with the scaling up of priority interventions (prevention and management of malaria
29 cases). Severe malaria, mainly due to *Plasmodium falciparum* infections, is responsible for nearly half
30 million deaths annually, affecting mostly children under five years old and pregnant women living in sub-
31 Saharan Africa, as well as non-immune travelers [1]. Although *P. falciparum* is the most prevalent and
32 dangerous species, other *Plasmodium* species including *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*
33 account for a non-negligible impact on human health. Malaria symptoms, ranging from cyclic febrile
34 episodes to life-threatening complications (severe anemia, respiratory distress and coma) are mainly
35 linked with the parasite development into human red blood cells (RBCs) [2]. Studying the complex host-
36 pathogen interactions are of major importance to decipher cellular and molecular mechanisms involved
37 in malaria infections and to develop more effective therapies and vaccine [3,4].

38

39 To date, many parasite proteins have been described as essential for *Plasmodium* parasites to
40 achieve its complex life cycle in the human host during various steps. One of the main challenges of the
41 malaria parasites for an effective proliferation and differentiation into the RBCs is to escape the human
42 immune system. The selection of highly polymorphic sequences at the end of some chromosomes (*i.e.*
43 subtelomeres) encoding variant polypeptides of multicopy gene families seems to explain how malaria
44 parasites have adapted to this barrier [5]. Some of these variant polypeptides have been shown to be
45 involved in host cell adhesion, notably in promoting parasite invasion into RBCs. However, the major role
46 of these variants, exposed on the surface of infected RBCs, is to ensure the antigenic variation and
47 therefore to circumvent the host immunity response. Among hundreds of adhesive proteins, three main
48 families are well-documented [6]. These include the *var* family encoding variant antigens *P. falciparum*
49 erythrocyte membrane protein 1 (PfEMP1), the subtelomeric variant open reading frame family (*stevor*)
50 encoding STEVOR proteins, and variant polypeptides from the repetitive interspersed family (*rif*)
51 encoding RIFINs [6]. PfEMP1, STEVOR, and RIFINs are responsible for characteristic protuberances on
52 the surface of the RBCs in association with sub-membranous network of knob proteins (Figure 1A). This
53 unique RBC membrane shape is known to promote the binding of infected erythrocytes to the
54 endothelium (cytoadherence), a major mechanism to circumvent removal of infected RBCs by the spleen
55 and the main pathophysiological phenomenon responsible for the severe forms of malaria [6]. Besides
56 this function, variant surface antigens also play a crucial role in regulating interactions of infected RBCs
57 with immune cells for dampening the host response.

58

59 In this respect, spectacular progresses had been done in the past years in our understanding of the
60 function of RIFINs, used by *P. falciparum* to escape the host immune system. More precisely, some RIFIN
61 variants were shown to be able to bind to either leucocyte immunoglobulin-like receptor B1 (LILRB1) or

62 leucocyte-associated immunoglobulin-like receptor 1 (LAIR1) [7-9] and inhibit the activation of LILRB1-
63 expressing immune cells. However, one of the missing pieces of the puzzle was to comprehensively
64 define the inhibitory function of RIFINs. This has been made recently in a striking study published by
65 Harrison and colleagues. They elucidated the structural basis by which RIFINs activate LILRB1 by
66 mimicking the binding mode of the natural ligand of LILRB1 for suppression of immune cell function
67 [10].

68

69 The *Plasmodium* RIFIN family is composed of approximately 150-200 members, structurally
70 categorized in two subtypes (A and B). Most of the RIFINs belongs to the A subtype. The canonical
71 domain architecture of *P. falciparum* type-A RIFINs consists of a C-terminal signal peptide (SP), a first
72 short variable domain (V1), a *Plasmodium* export element (PEXEL), a constant semi-conserved domain,
73 a 25 amino acid-long insertion-deletion sequence (indel), a second large variable domain (VD), a
74 transmembrane region (TM), and finally a basic terminal sequence (BTS) (Figure 1B). In their study [10],
75 the authors demonstrated first that only the variable region of RIFINs binds to LILRB1. Intriguingly, they
76 found that RIFINs binding affinities for LILRB1 are comparable to those previously observed with MHC
77 class I molecules. Structure resolution approaches revealed that the LILRB1-binding region to RIFINs is
78 composed of a loop linking a couple of helices albeit the contact surface of LILRB1 with RIFINs is located
79 within the two N-terminal immunoglobulin-like domains (ILD1 and ILD2, Figure 1C). These structural
80 predictions were then tested in a cellular context by using a reporter system in which fluorescence is
81 emitted upon LILRB1 binding, and the authors confirmed that the predicted contact surface is involved
82 in the induction of LILRB1-mediated signaling. Second, through mutagenesis studies, they provided final
83 evidences demonstrating that RIFINs preserve their intrinsic function of adhesins despite high
84 polymorphisms of the *rif* genes selected for promoting antigenic variation, and thus preventing the host
85 immune detection, similar to what was observed for PfEMP1 proteins. They also indicated a common
86 binding site for LILRB1 of the RIFIN and the MHC class I molecules (here HLA-A2) despite their very
87 different structures (Figure 1D). Third, they proposed, by using a supported lipid bilayer system for
88 triggering NK cell activation by antibody-dependent cell-mediated cytotoxicity (ADCC), an hypothetical
89 mechanism by which this 3D similarity with MHC class I molecules is used by RIFINs at immunological
90 synapse, formed between immune cells (mainly CD4⁺ T cells and NK) and infected RBCs to prevent ADCC
91 (Figure 1E).

92

93 In summary, Harrison and colleagues' findings nicely highlight the structural basis underlying RIFINs
94 interaction with the prominent inhibitory immune receptor LILRB1. Importantly, this dampening function
95 of RIFINs is ensured by a dedicated LILRB1-binding surface that commonly displays strong antigenic
96 variation to avoid immune detection. This enlightening article provides additional evidences that *P.*
97 *falciparum* multigene families of adhesins has evolved to disrupt the activation of immune cells, hereby

98 mimicking the structure of the natural ligand of LILRB1, *i.e.* MHC class I molecules. This study points out
99 once again how *P. falciparum* parasites have deployed a plethora of strategies to survive in the human
100 host and therefore to sustain *P. falciparum* life cycle in endemic areas.

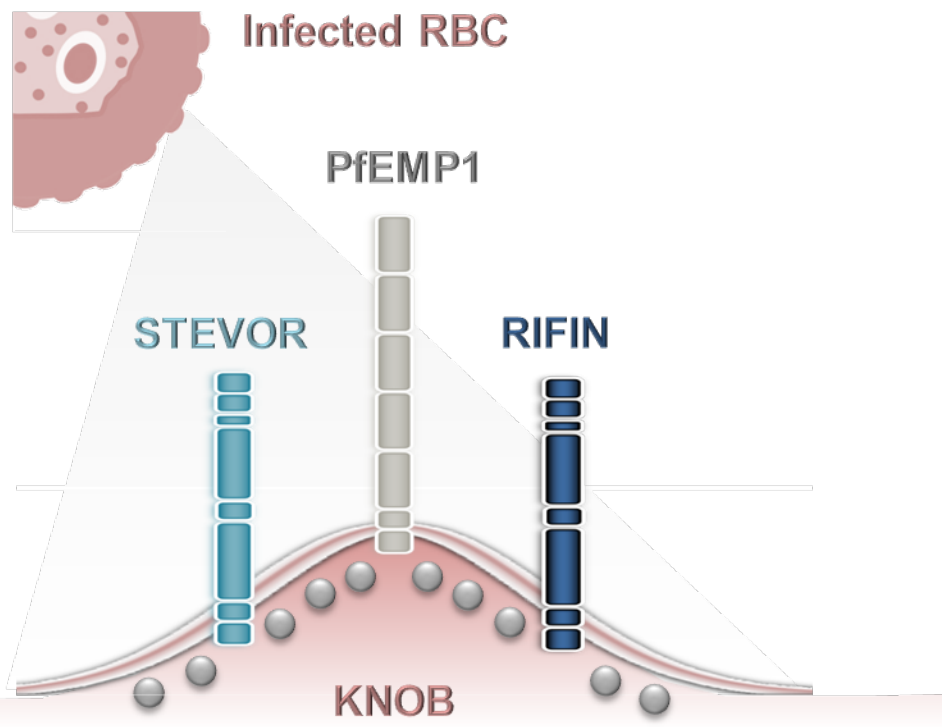
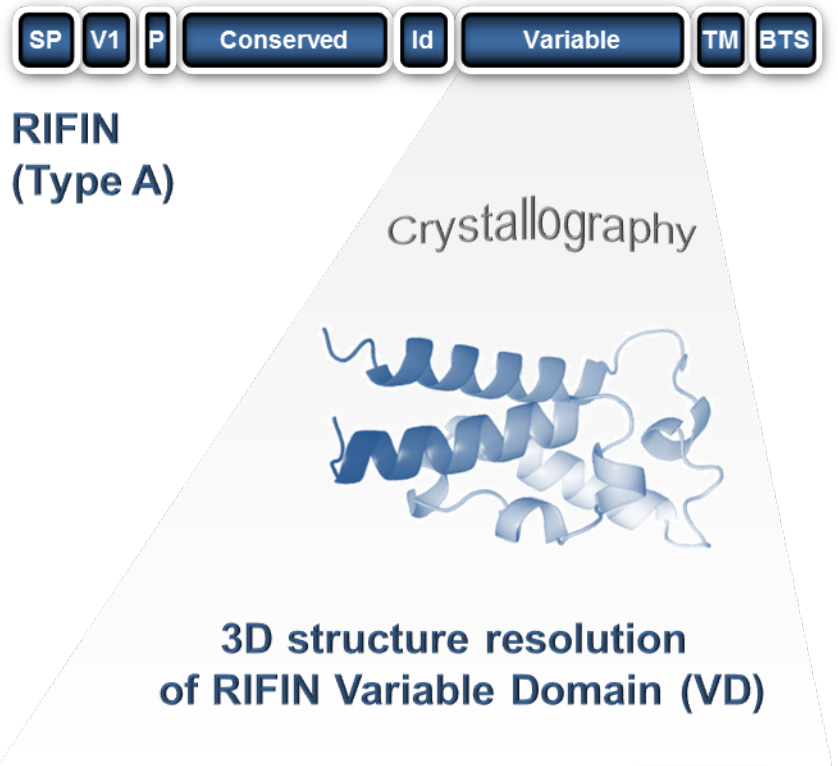
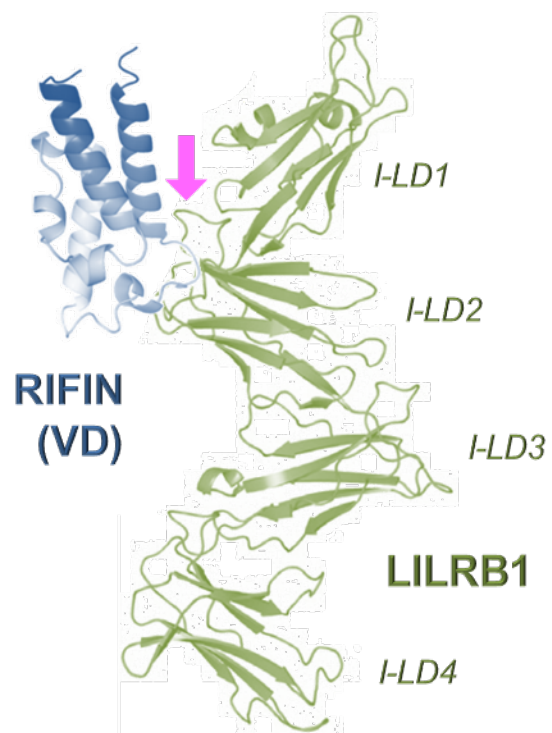
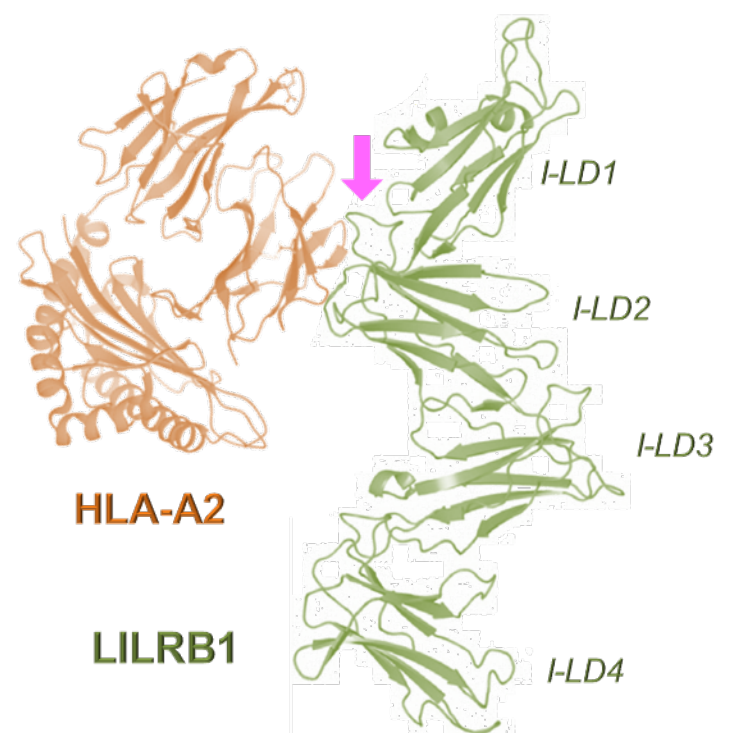
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122

123 **Figure 1. Structural basis for RIFIN-mediated activation of LILRB1 in *falciparum* malaria.**
124 **A.** Schematic representation of the three main families of adhesive proteins on the surface of infected
125 RBCs during the erythrocytic cycle: the *var* family encoding variant antigens *P. falciparum* erythrocyte
126 membrane protein 1 (PfEMP1), the subtelomeric variant open reading frame family (stevor) encoding
127 STEVOR proteins, and variant polypeptides from the repetitive interspersed family (rif) encoding RIFINs.
128 PfEMP1, STEVOR, and RIFINS form characteristic protuberances on the surface of erythrocytes in
129 association with sub-membranous network of knob proteins. **B.** Gene structure of the *Plasmodium* RIFIN
130 family. This family is composed of approximately 150-200 members and structurally categorized in two
131 subtypes (A and B). The canonical domain architecture of *P. falciparum* type-A RIFINs (the most frequent
132 subtype) consists of a C-terminal signal peptide (SP), a first short variable domain (V1), a Plasmodium
133 export element PEXEL (P), a constant semi-conserved domain, a 25 amino acid-long insertion–deletion
134 sequence indel (Id)), a second large variable domain (VD), a transmembrane region (TM), and a basic
135 terminal sequence (BTS). **C.** Mapping of LILRB1-binding region of RIFINs. This region is composed of a
136 loop linking a couple of helices. The contact surface of LILRB1 with RIFINs is located within the two N-
137 terminal immunoglobulin-like domains I-LD1 and I-LD2. **D.** Mapping of LILRB1-binding region of MHC
138 class I molecules (here HLA-A2). LILRB1 is expressed on various immune cell types, including T cells, B
139 cells, natural killer (NK) cells and monocytes, and cells that are involved in suppressing B cell responses.
140 **E.** Schematic representation of the hypothetical mechanism of the suppression of NK cell activation by
141 antibody-dependent cell-mediated cytotoxicity (ADCC). The 3D similarity between MHC class I molecules
142 and RIFINs is used by the RIFINs at immunological synapse, formed between immune cells and infected
143 RBCs to prevent ADCC.

A**B****C****D****E**