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Blood Profile of Lymphocyte Lineage Determining Transcription Factor Gata3 May Influence Malaria Disease Outcome of Children in the South of Benin

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Abstract

Background: *Child morbidity in African countries including the Republic of Benin, is mostly attributed to parasitic infectious diseases involving malaria. Molecular disorder often underlies the vulnerability of children immune system to infectious diseases. This reduces the ability of immune system to combat appropriately exogen organisms including parasites larva, bacteria or viruses. GATA-3 is a nuclear protein expressed by immune cells and belongs to a family member of the lymphocyte CD4 lineage determining transcription factors inducible by retinoic acid. Thus, GATA3 is one of the main regulators of lymphocyte T-helper 2 (Th2) cell differentiation into mature CD4+ T cells that mediate immunity to combat exogen microorganism involving plasmodium falciparum (pf). The objective of the study is to investigate if children with low or absence of GATA3 expression will be more vulnerable to pf infection and malaria.*

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Methods: *This study has received an institutional ethical approval. Preliminary study carried out on cell lysates of peripheral white blood cells isolated from blood samples used for pf counts in Benin Zonal hospital of Calavi/So-Ava diagnosis laboratory involving eighteen children (5-9 years) admitted for fever associated or not to malaria. Immunoblotting (western blot) technic was used to evaluate GATA3 expression in all samples. The presence of pf was determined with microscopic observation of blood thick smears stained with Giemsa.*

Results: *Among the eighteen samples, normal expression of GATA3 was observed in ten, low expression in six while no expression was observed in two samples. Overall, seven samples were positive for pf counts ranging from 350-1500 per mm^3 of red blood cells. Infection with pf was not observed in eleven samples.*

Conclusion: *Immune system of children with low GATA3 and high level of pf count will be more vulnerable to infection. Thus, the absence of GATA3 transcription factor could influence the outcome of malaria disease and render children too weak to fight pf infection. The absence of GATA3 may also render them vulnerable to develop allergy or lymphoma in the future.*

Keywords

Nuclear protein; GATA3 transcription factor; Lymphocyte differentiation; Plasmodium falciparum; Malaria outcome.

List of abbreviations

CLERB-UP: Comité local d'éthique pour la recherche biomédicale de l'université de Parakou ; HRP : Horseradish Peroxidase; KCl : potassium chloride; NaCl: Sodium chloride; NaF: sodium fluoride; NaN3: Sodium azide; PBS : phosphate Buffered Saline; *pf: plasmodium falciparum*; PMSF: Phenyl-Methyl-Sulfonyl Fluoride; SDS: sodium dodecyl sulfate; TBS: Tris Buffer Saline; TBST: Tris Buffer Saline plus Tween-20; Tris-HCl: Tris-Hydrochloride.

Background

Child morbidity in African countries including the Republic of Benin is often associated to parasitic infection [1]. Malaria disease is due to infection with plasmodium falciparum (pf) and ranked number one cause of child death. The predisposition of children to infectious diseases could be due to molecular disorders reducing the ability of immune system to combat efficiently exogenous microorganisms including viruses, bacteria or parasites [2]. GATA-3 is a zinc finger nuclear protein and a transcription factors expressed by immune cells from the state of hematopoietic stem cells to the state of mature lymphocyte T cells [2]. GATA3 belongs to the member of the GATA transcription factors involved in lineage determination through binding on (A/T) GATA (A/G) site positioned within target gene promotor [3]. During the process of positive selection and CD4/CD8 lineage commitment, the upregulation of GATA-3 determine CD4 lineage differentiation [4-6]. Naïve CD4 T cells can differentiate into at least two different types of lymphocyte T helpers Th1 and lymphocyte Th2 cells, upon antigen stimulation by the antigen presenting cells while the cell

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regulation activity of GATA-3 promotes T-helper 2 (Th2) cell differentiation towards mature CD4+ T cells all of which is crucial to battle viral and parasite infection [7]. Th2 cells producing IL-4, IL-5 and IL-13, mediate humoral immunity against extracellular pathogens (e.g. pf) and a deficiency of GATA-3 induced in animals' impacted CD4 cells development making them vulnerable to extracellular pathogens [7]. Immunity against intracellular pathogens (viruses, bacteria) is mediated by Th1 induced by IFNγ while IL-4 induces Th2 differentiation through the up-regulation of GATA3 [8-11].

In summary, the ability of an organism to defend itself against infectious and inflammatory diseases depends upon the expression of GATA3 in lymphocytes. The overexpression of GATA3 will direct CD4 cells toward lymphocyte Th2 lineage to fight extra cellular parasites or to initiate asthma or allergic diseases while low expression of GATA3 will direct CD4 cells toward Th1 to act against intracellular pathogens. Individual with low expression of GATA3 in T cells will be more vulnerable to parasitic infection. The reasons why some children are more vulnerable to malaria are not well defined. This preliminary study will verify the expression profile of GATA3 in a small sample of sick children in the south of the Republic of Benin to help to project disease outcome.

Methods

Sample study

Preliminary study carried out on cell lysates of peripheral white blood cells isolated from blood samples used for pf counts in Benin Zonal hospital of Calavi/So-Ava diagnosis laboratory involving eighteen children (5-9 years) admitted for fever associated or not to malaria. Immunoblotting (western blot) technic was used to evaluate GATA3 expression in all samples. The presence of pf was determined with microscopic observation of blood thick smears stained with Giemsa. The western blotting technic used to assess GATA3 expression in all samples was done in the laboratory of the Unit of Biochemistry and Molecular Biology (UBBM) of the University Abomey Calavi (UAC). The presence of pf was determined with microscopic observation of blood thick smears stained with Giemsa as previously reported [1].

Reagents

NaCl, KCl, Tris-Base, glycine, Sodium Dodecyl Sulfate (SDS), Tween®20 were purchased from Omnipur®, USA. West Dura Extented duration Substrate (Pierce) was purchased from Thermo Scientific, USA. Antibody directed against GATA3 was from Santa Cruz Biotechnology, USA. Giemsa was from Sigma-Aldrich, USA. Blood withdrawal EDTA-tubes (5 ml), needles and gloves were from hospital pharmacy in Benin.

White blood cells (WBC) processing and protein extraction

Following the use of plasma of 3 ml blood collected in 5 ml EDTA-tube, the remaining blood

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cells was spin down with 2500 rpm at 4°C for 10 min by the technicians. The remaining plasma on top was discarded and white blood cells (WBC) congregated in the white buffy coat above the pellet of red blood cells were collected in a 1.5 ml Eppendorf tubes. WBC were rinsed twice with ice cold PBS containing protease inhibitor cocktails followed by a with centrifugation at 1300 rpm at 4°C for 5 min. Pellet of WBC was suspended in cell lysate buffer composed with a mixture of tris-HCl (50 mM, pH 7.9), NaCl (150 mM), EDTA (0.1 mM), 1 % NP-40, DTT (0.5 mM), PMSF (0.5 mM), NaF (30 mM) and 0.5 % protease inhibitor cocktail. All Eppendorf tubes containing rinsed WBC pellet were kept on ice for 30 min for full cell lysis and collection of protein extracts. Protein samples were boiled in SDS sample buffer for 5 min before freezing and storage at -20°C until needed for analysis with immunoblotting (western blot) technics. Prior to immune blotting, protein samples were boiled again before loading on 10 % SDS-poly-acrylamide gels followed by electrophoretic migration at 100 volts for 90 min. The electrophoresis running buffer was tris-Base/glycine buffer composed of Tris-Base (25 mM), glycine (192 mM) and 0,1% SDS. After electrophoresis, the proteins were transferred from the gel onto nitrocellulose membranes at 35 volts for 90 min in a transfer buffer composed of Tris-Base (25 mM), glycine (192 mM) and 20 % methanol. The membranes were pre incubated in a blocking buffer composed of 5 % skim milk freshly diluted in Tris-buffered-saline (25 mM Tris-base, 150 mM NaCl, 2 mM KCl) and 0.1 % Tween-20 (TBST) for 30 min at room temperature or overnight at 4°C. The membranes were then incubated in primary antibody anti GATA3 or anti β-actin (produced in mouse), previously diluted in 1% skim milk-TBST. The incubation in the primary antibody solution was done for 1h at room temperature. For the revelation of GATA3 or β-actin the secondary antibody used was HRP-conjugated rabbit anti-mouse. The incubation in the secondary antibody solution was done for 1h at room temperature. The blots were washed 4 times for 15 min with TBST. To identify GATA-3 or β-actin expression profile, the membranes, were incubated for 3 min in Super Signal West Dura Extended Duration Substrate and exposed to x-ray films. The films were developed in a developer to reveal the dark bands corresponding to GATA-3 or β-actin proteins on the membranes. The analysis of ß-actin was used as a loading control.

Thick blood smear and pf counts

Whole blood thick smear (20 µl) was done on microscopic glass slide, air dried, fixed with methanol and stained with 10% Giemsa before observation under Nikon microscope with 100X objective. White blood cells red blood cells and pf (parasites and gametocytes) were counted. The counting of pf was done per 200 WBC and results were given as parasites/µl of blood or mm3.

Ethical Considerations

The guidelines of the declaration of Helsinki were followed. For all blood works and laboratory analyses informed consent were obtained from the parents. The procedures

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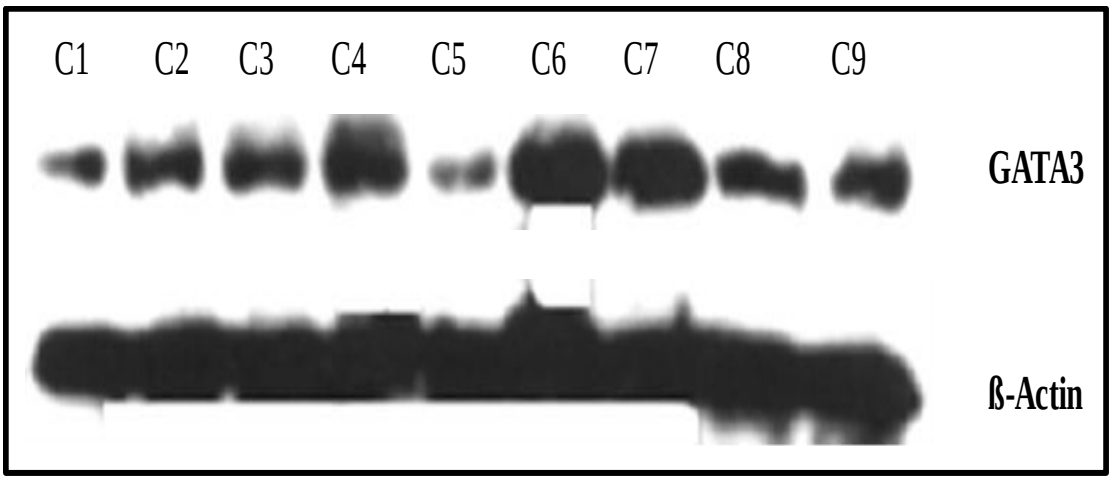
followed in this study were also in accordance to our institute ethical guidelines on laboratory research and data obtained could not be traced to individuals. Institutional Ethical approval (0086-CLERB-UP) was obtained for this research work. CLERB-UP in french means « Comité local d'éthique pour la recherche biomédicale de l'université de Parakou ».

Results

Analyses of GATA3 in white blood cell lysates along with pf counts in thick blood smears: One example of western blotting showing GATA3 expression in white blood cell lysates is displayed (Figure 1).

High expression of GATA3 is observed in 3 children (C4, C6, C7), low expression of GATA3 is observed in 7 children (C1, C5, C10, C12, C14, C15, C16), absence of GATA3 is observed in 3 children (C11, C17, C18) and GATA3 is normally expressed in 5 children (C2, C3, C8, C9, C13).

Figure 1: Western blotting showing an example of GATA3 expression profile in 9 children. C1 and C5 displayed low expression of GATA3.



Western blot profiles of GATA3 for the 18 samples are summarized in table 1 as follows: absence of GATA3 expression (A), low GATA3 expression (L), normal GATA3 expression (N), high GATA3 expression (H), compared to β-actin expression. The data of *Plasmodium falciparum (pf) counts* in thick blood smears along with GATA3 expression profile is presented (Table 1).

Plasmodium infection in blood: Microscopic observation documented the presence of pf in red blood cells and the results are shown in table 1 along with GATA3 expression profile. Overall, seven samples are infected with pf (7/18 samples). One sample with high expression of GATA3 has high pf count (C4 with 1500 pf/mm^3) as shown on table 1. The presence of GATA3 in samples C1-C4 will induce lymphocyte T CD4 to destroy pf while the absence of

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GATA3 in C17-C18 will impair CD4 formation. In presence of high pf counts GATA3 expression is increased in sample C4 (Table 1).

Table 1: Summary of GATA3 western blot result and *pf* count in the 18 samples

Scrambled Sample		
N°	GATA3	Pf count on thick blood smears (pf/mm3)
C1	L	850
C2	N	350
C3	N	840
C4	H	1500
C5	L	negative
C6	H	negative
C7	H	negative
C8	N	negative
C9	N	negative
C10	L	negative
C11	A	negative
C12	L	negative
C13	N	negative
C14	L	negative
C15	L	negative
C16	L	850
C17	A	840

The status of GATA3 was represented by letters. A: absence of GATA3, L: low expression of GATA3; N: normal expression of GATA3; H: high level of GATA3 expression in comparison to the expression of the β-actin control.

The total loss of GATA3 was observed on 3/18 samples and low GATA3 was observed on 7/18 samples normal level of GATA3 was observed in 5/18 samples and high expression of GATA3 was observed in 3/18 samples.

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Discussion

Children with samples C1, C16, C17 and C18 will be very sensitive to *pf* infection and malaria disease because the absence of GATA3 will impair the induction of lymphocyte T CD4 cells to fight *pf* infection. Children with sample C11 has no GATA3 and may be at risk of chronic malaria if infected by *pf*. Children with samples C2, C3 and C4 will have enough production of lymphocyte T CD4 cells to fight pf infection and malaria disease by the immune system**.** Due to the involvement of GATA3 in extra cellular pathogen responses, the children with low expression of GATA3 or absence of GATA3 will have difficulties to eliminate *pf* parasites from the blood stream in contrast to samples with normal expression of GATA3. The exact molecular disorder upstream the absence of GATA3 is not known but will be investigated further. Thus, children with samples C1, C16, C17 and C18 will be very sensitive to *pf* infection and malaria disease because the absence of GATA3 will impact the induction of lymphocyte T CD4 cells to fight *pf* infection. Children with sample C11 has no GATA3 and may be at risk of chronic malaria if infected by *pf*. In contrast, children with samples C2, C3 and C4 will have enough production of lymphocyte T CD4 cells to fight *pf* infection and malaria disease by the immune system. Children with GATA3 deficient T cells may have defective immunity responses toward parasitic infection, viral infections, alloantigen, and cancer cells [13,15,16]. All children with total absence of GATA3 (C11, C17 and C18) could also be at risk to develop diseases including lymphoid malignancies later in life [13,15,16-19]. It was reported that GATA3 transcript is under the control of the RNA binding protein HuR and GATA3 coordinates the expression of Th2 genes at both the epigenetic and transcriptional levels [15-17]. The mechanism of deficiency in GATA3 was linked to either DNA polymorphism or epigenetic silencing in developed countries, but in the reality the actual mechanism should be investigated individually to propose personalized treatments to sick children [14,19,20]. Many conceivable mechanisms could be investigated including gene alteration, gene mutation, epigenetic modification, or protein degradation [17]. We have discovered some DNA polymorphism of GATA3 genes in different study that will be published soon. Unlike genetic mutation that could lead to the absence of GATA3, the epigenetic downregulation of GATA3 could be corrected with specific medication that inhibits epigenetic events. Recent studies have reported the role of micro-RNA in the downregulation of GATA3, accordingly miR-24 and miR-27 limit Th2 responses through targeting IL-4 and GATA3 in both direct and indirect manners [17]. Aberrant GATA3 expression was detected in classical Hodgkin lymphoma in African children [18]. Although lymphoma cases are currently rising among African, biomarker is not yet popular to pre-diagnose children at risk of developing lymphoid malignancies later in life [19]. Previous study has reported that lower expression of GATA3 and T-bet correlates with the downregulation of IL-10 in severe falciparum malaria [20]. According to our data, not all *pf* infected children had low GATA3. It Means that the presence of GATA3 may help to boost the immune system toward CD4 type to fight *pf* invasion and prone quicker recovery from malaria disease but may not regulate directly GATA3 expression. Our study showed that

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GATA3 was downregulated in several samples and could be used as biomarker in Benin for medical survey among children to determine their susceptibility to *pf* infection or blood malignancies during childhood. This differential approach combining GATA3 level and *pf* infection may help pediatrician to update malaria treatment to reduce child morbidity and mortality.

Conclusion

Overall, the assessment GATA3 profile could help to predict children at risk of infections including *pf* leading to malaria or at risk of developing lymphoid malignancies in the future and could also be used as biomarker for proper personalized medicinal treatments.

Declarations

Ethical declaration:

Ethics Approval and Consent to Participate: Institutional ethical committee ((0086-CLERB-UP) approves this pilot study. For all blood works and laboratory analyses informed consent where obtained from the parents. The procedures followed in this study were in accordance of Helsinki declaration and in accordance of our institute ethical guidelines on laboratory research. The data obtained could not be traced to individuals.

Consent for publication: Not applicable.

Availability of data and supporting materials: All data analyzed during this study are included in this published article

Competing interests: No competing interest is to be reported.

Conflict of Interest: This study is a collaboration effort between or laboratory BMCN/UBBM, the Zonal Hospital Calavi/So-Ava. No conflict of interest is to be reported by the authors.

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Authors' contributions

1 CDC: PhD, PMH, Mentor and principal investigator who designed, oversee the study and wrote the manuscript.
2 VWT: PhD performed all bench works.
3 OAD: MS, Head of the Unit of Quality Assurance and Evaluation in Zonal University Hospital of Abomey-Calavi/ Sδ-Ava (CHUZ-AS) involved in the study.

4 IDD: MD, Pediatrician in Zonal University Hospital of Abomey-Calavi/ Sδ-Ava (CHUZ-AS) involved in the study.
5 AS: PhD, Former Director of UBBM involved in the study.

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