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Alteration of Lymphocyte Phenotype and Function in Sickle Cell Anemia: Implications for Vaccine Responses

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Abstract

Individuals with sickle cell anemia (SCA) have increased susceptibility to infections, secondary to impairment of immune function. Besides the described dysfunction in innate immunity, including impaired opsonization and phagocytosis of bacteria, evidence of dysfunction of T and B lymphocytes in SCA has also been reported. This includes reduction in the proportion of circulating CD4+ and CD8+ T cells, reduction of CD4+ helper : CD8+ suppressor T cell ratio, aberrant activation and dysfunction of regulatory T cells (T_{reg}), skewing of CD4+ T cells towards Th2 response and loss of IgM-secreting CD27+$IgM^{high}IgD^{low}$ memory B cells. These changes occur on the background of immune activation characterized by predominance of memory CD4+ T cell phenotypes, increased Th17 signaling and elevated levels of C-reactive protein and pro-inflammatory cytokines IL-6 and TNF-α, which may affect the immunogenicity and protective efficacy of vaccines available to prevent infections in SCA. Thus, in order to optimize the use of vaccines in SCA, a thorough understanding of T and B lymphocyte functions and vaccine reactivity among individuals with SCA is needed. Studies should be encouraged of different SCA populations, including sub-Saharan Africa where the burden of SCA is highest. This article summarizes our current understanding of lymphocyte biology in SCA, and highlights areas that warrant future research.

Keywords

T cells; B cells; phenotype; function; vaccine; sickle cell anemia

INTRODUCTION

Individuals with Sickle Cell Anemia (SCA), the homozygous (HbSS) sickle cell disease (SCD), are at an increased risk of invasive bacterial infections[1–3]. Particularly, the risk is

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high for infection with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*[2–4]. Pneumococcal pneumonia, septicemia and meningitis in particular are important causes of morbidity and mortality in individuals with SCA, especially at younger age[3, 5, 6]. The use of penicillin prophylaxis has reduced the mortality attributable to invasive pneumococcal disease in children with SCA[7–9]. However, for more sustainable control of infections, engagement of the immune system via vaccination is believed to be the most durable and cost effective approach[10, 11]. To this effect, pneumococcal vaccines have been the standard of care for individuals with SCA in developed countries since their introduction[8, 12, 13]. In sub-Saharan Africa, where the burden of SCA is highest, pneumococcal vaccines are currently being introduced. Besides bacterial infections, children with SCA in sub-Saharan Africa are also at risk of mortality from malaria which is endemic in the region[14–16]. Thus, besides vaccines against bacterial infections, introduction of a malaria vaccine could have enormous impact on mortality in children with SCA in sub-Saharan Africa[17].

The current recommendations for usage of vaccines in children with SCA are based on efficacy trials done mostly in individuals without SCA[12, 18–20]. Limited studies conducted thus far have indicated adaptive immune abnormalities in individuals with SCA[21–29]. These abnormalities, including reduction in the proportion of circulating CD4+ and CD8+ T cells, dysfunction of regulatory T cells and impaired B cell IgM secretion[23, 25–27], occur concurrent with increased immune activation[25, 30–40] and may affect vaccine reactivity in individuals with SCA. Thus, immune abnormalities in SCA may potentially explain incidences of impaired magnitude or duration of response to vaccines reported in individuals with SCA[26, 41–45]. Of note, critical studies reporting adaptive immune changes in SCA were done among SCA populations in the United States and Europe[23, 25–27]. It is however possible that geographic differences in lymphocyte function may also occur between SCA populations in the West compared to those in sub-Saharan Africa due to differences in environmental exposures, including malaria and other infections which are endemic in sub-Saharan Africa[15], and have an impact on the immune system[46, 47]. Indeed, regional differences in responsiveness to Bacille Calmette-Guerin (BCG) between recipients in the West and those in sub-Saharan Africa have previously been observed[48–50]. Specific regional consideration is therefore essential to effective vaccine planning, since the sub-Saharan region faces a double challenge—the rates of both SCA and endemic infectious disease, including malaria, are the highest in the world[15], and both factors could directly influence vaccine reactivity.

Currently, there is a critical shortage of insight on the immune status, especially adaptive immunity, in SCA. This shortage of insight limits our understanding of the potential for vaccine reactivity in SCA. It is precisely this acute gap in knowledge that calls for a detailed review of what is currently known about the immune function in SCA. This review summarizes our current understanding of the immune phenotype and function in SCA, and highlights areas that warrant future research. Thorough understanding of the immune function in SCA may lead to optimization of care, including delivery of vaccines in individuals with SCA, aiming at overcoming the burden of infections in SCA.

INNATE IMMUNE DYSFUNCTION IN SCA

Impairment of the innate immunity is the most well described immune dysfunction in individuals with SCA. Part of the dysfunction has been shown to include increased peripheral blood neutrophil count (granulocytosis), which often accounts for leukocytosis in SCA.[37, 51, 52]. However, the increased neutrophils are mostly dysfunctional due to impaired chemotaxis, migration and killing ability[28, 52, 53]. Impairment of the alternate pathway of complement activation through qualitative and quantitative deficiencies of factors B and C3 has also been reported[54, 55], although this observation has not been consistent between studies[27, 56].

Spleen and Innate Immune Dysfunction in SCA

Most of the innate immune changes in SCA are a manifestation of reduced splenic function (hyposplenism), which can occur in the context of atrophied or enlarged spleen[53, 57, 58]. This loss of splenic function in SCA has been attributed primarily to repeated sickling in the spleen with eventual destruction of the architecture and function of the spleen[57, 58]. The BABY HUG study demonstrated that loss of splenic function starts early on during infancy in individuals with SCA[59]. Splenic filtration function is often compromised as well in this setting, leading to decreased ability for trapping and removing bacteria from the circulation[58, 60]. Overall, SCA patients with hyposplenism show reduced opsonophagocytic activity and ability to clear bacteria from the blood[28, 52, 57, 58]. The loss of splenic function and ensuing reduction in opsonophagocytic activity is the most well accepted cause for the increased risk of infection with encapsulated bacteria in SCA[58]. In the absence of interventions, including timely vaccinations and proper coverage with prophylactic antibiotics, immune impairment due to hyposplenism in SCA can results in severe and life-threatening infections[58, 61].

ADAPTIVE IMMUNE DYSFUNCTION IN SCA

High rates of alloimmunization, connective tissue diseases and transplant rejections[62–66], as well as incidences of aberrant vaccine reactivity[26, 41–45], have bought to surface adaptive immune abnormalities in SCA. Currently, however, little has been done to characterize T and B lymphocyte phenotype, function and contribution to chronic inflammatory diseases in SCA. Limited studies done indicate that abnormalities in both T and B cells occur in SCA[21–29]. These abnormalities may be induced by SCA disease itself, or may arise as a result of complications of its treatment with repeated blood transfusions. A focus on adaptive immune abnormalities in SCA will refresh our outlook towards SCA as an immune disease, and may open up novel research on immunity in SCA as well as lead to development of newer approaches in combating the immune derangement, inflammatory diseases and improving vaccine outcomes in individuals with SCA.

Disease-Induced Changes in T and B Lymphocytes

The number of circulating T cells was found to be highly variable between individuals with SCA at steady state[21–23, 29]. However, most studies have reported a reduction in the proportion of circulating CD4+ and CD8+ T cells in SCA[21, 23, 27, 29], with normal or

increased absolute CD4+ and CD8+ T cell count[22, 27,37], particularly of the memory phenotype[37]. The reduction in the proportion of circulating CD4+ and CD8+ T cells was shown to be more profound in the presence of splenic defects and vaso-occlusive crises, where patients also show reduced CD4+ helper : CD8+ suppressor T cell ratios[22, 29]. In vaso-occlusive crises, there is also an increase in interleukin-4 (IL-4) secretion, suggesting a shift of CD4+ T cell response towards a T helper 2 (Th2) phenotype[29]. This polarization is further supported by reduced expression of the Th1 transcriptional factor T-bet and corresponding Th1 cytokines gamma interferon (INFγ) and IL-2 by CD4+ T cells in SCA[24, 39]. The impairment of antiviral Th1 response may explain the increased risk of hospitalization from influenza infection among children with SCA compared to those without SCA[67]. The frequency of regulatory T cells (T_{reg}) in patients with SCA was found to be variable between studies[25, 37, 68]. A recent study by Vingert, B. *et al* compared T_{reg} phenotype in individuals with and without SCA, showing that T_{reg} in SCA were more activated and expressed high levels of CTLA-4[25]. Similarly high CTLA-4-expressing T_{reg} were shown to mediate suppression of pneumococcal-specific CD4+ T cells acquired through nasal carriage[69], suggesting that the activated and partially dysfunctional T_{reg} in SCA may modulate host immunity and susceptibility to invasive pneumococcal disease. Whether these T_{reg} also impact the vaccine-induced immunity to pneumococcus and other pathogens is yet to be studied. Building on the emerging insights, further characterization of these CD4+ T cell subsets, especially from SCA populations in sub-Saharan Africa, is much needed. This will help elucidate the functional status and role of the critical CD4+ T cells in the immune defense against infections in SCA.

Unlike T cells, the proportions of circulating B cells in SCA are generally unaltered[23, 26, 27], although modest increases in B cells have been observed[21, 37]. However, functional abnormalities in humoral immunity have been reported. These include reduction in antigen-specific B cell proliferative response and IgM secretion, with preservation of other classes of immunoglobulins[26, 27]. The selective loss of IgM secretion is thought to occur due to loss of the non-T cell dependent CD27+$IgM^{high}IgD^{low}$ "IgM memory B cells" that are normally resident in the marginal zone of the spleen[57, 58, 70]. Loss of splenic function is thought to be the main driver of the impairment in IgM secretion since individuals without SCA who have undergone splenectomy show similar immunological alteration[27]. Impairment in B cell response in individuals with SCA has been shown to result in loss of IgM response to an influenza vaccine[41] and significant reduction in the number of antigen-specific immunoglobulin secreting cells following vaccination with a pneumococcal polysaccharide vaccine[26]. Beside IgM memory B cells, more insight is also needed regarding other B cell populations, namely the naïve, pre-germinal center, germinal center, plasma cells and other B cell memory subtypes, to establish their contribution to immunity against infections in SCA[71].

Among individuals with SCA, the observed immunological abnormalities vary depending on severity of disease. Unlike individuals with severe disease, those with mild SCA may have normal immunological parameters, with the exception of serum opsonization activity which is often impaired in severe as well as mild disease[28]. This variability is consistent with the considerable heterogeneity in the genetic makeup of individuals with SCA that impacts disease severity[72–75].

Spleen and Adaptive Immune Dysfunction in SCA

As is the case with innate immune dysfunction, most disease-induced changes in adaptive immunity in SCA are attributed to hyposplenism[22, 26, 27, 57, 58, 61, 76]. Since loss of splenic function begins early on during infancy[59], it is possible that adaptive immune dysfunction begins early on in children with SCA. Because critical IgM memory B cells require functioning spleen, patients with functional asplenia and hyposplenism, or those who have undergone splenectomy, experience loss of the non-class switched CD27+IgM^{high}IgD^{low} IgM memory B cells[27, 57, 58, 76]. The loss of splenic tissue has been associated with impaired IgM response following immunization with an influenza vaccine in individuals with SCA[41]. Similarly, the spectrum of T cell derangements in SCA, including reduction in the proportion of circulating CD4+ and CD8+ T cells, is highly associated with asplenia, hyposplenism or splenectomy[22]. The persistence of immune derangement following splenectomy in patients with SCA is in contrast to other blood disorders such as hereditary spherocytosis. In the latter, most hematological and immunological parameters, with the exception of reduced IgM and soluble CD8 (sCD8) secretion, are usually corrected 3 to 6 months following splenectomy[27, 77, 78]. More studies are needed to fully characterize the impact of hyposplenism and splenectomy on lymphocyte phenotype and function in SCA. Areas of interest include specific T and B cell subsets alteration, and kinetics of infection- and vaccine-elicited cellular and humoral immune responses during hyposplenism and following splenectomy in individuals with mild as well as severe SCA.

Transfusion-Induced Changes in T and B Lymphocytes

Patients with SCA who are recipients of multiple blood transfusions for the treatment of severe anemia or primary stroke prevention have an additional risk for immune derangements[79–81]. These derangements have been observed in the presence or absence of alloimmunization. Regardless of alloimunization status, patients with SCA recipients of multiple blood transfusions were found to have increased proportion of central memory CD4+ T cells[39], reduced CD4+ helper : CD8+ suppressor T cell ratios and impaired natural killer (NK) cell activity[82]. The reduction of CD4+ helper : CD8+ suppressor T cell ratio likely represents normal immune response to multiple blood transfusions as it has also been observed in individuals with other blood disorders necessitating repeated blood transfusions[82–84]. The immunomodulation brought about by repeated blood transfusions was linked to reduced responsiveness of children with SCA to H1N1 vaccine[45], and is hypothesized to contribute to increased infection risk[81, 85, 86].

Repeated blood transfusions can result in alloimmunization in individuals with SCA. In routinely cross-matched blood, alloimmunization normally occurs via sensitization to non-ABO and non-Rhesus D antigens, including Rhesus antigens C and E, Kidd antigen Jk^{b}, Duffy antigen Fy^{a} and MNS antigen S on red blood cell (RBC) surfaces[39, 63]. A number of lymphocyte abnormalities have been observed in individuals with SCA who are alloimmunized, although it is not clear whether they are a cause or effect of alloimmunization. The predominant immunological alterations observed in alloimmunized SCA individuals is the skewing of CD4+ T response towards Th2 and Th17 phenotypes with increased IL-4 and IL-17 expression, respectively, and reduction of T_{reg} activity[30, 39, 87, 88]. The increase in Th2 signaling with elevated IL-4 secretion is similar to that observed in

individuals with SCA during vaso-occlusive crises[29]. Alloimmunization has also been linked with an accentuated increase in the proportions of the central and effector memory CD4+ T cells in patients with SCA[36].

To date, little has been done to characterize follicular helper CD4+ T cells (T_{fh}) in individuals with SCA. These cells express inducible T cell co-stimulator (ICOS) and CD40 ligand (CD40L), and secrete IL-21 and IL-4 which are potent stimulators of B cell differentiation and immunoglobulin secretion[89–91]. T_{fh} cells were shown to be play a pivotal role in responsiveness to HIV, hepatitis B, influenza and malaria vaccines[92–95]. Different transitional stages of T_{fh} cells are currently recognized based on their surface expression of the chemokine receptors CXCR5 and CCR7, as well as programmed death-1 (PD-1)[91]. Increased frequency of $PD1^+CXCR5^+$ T_{fh} cells has been observed in individuals with SCA who were not alloimmunized[39]. Among individuals with SCA who were alloimmunized, an increase in IL-21 secretion by $PD1^+CXCR5^+$ T_{fh} cells and novel "T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory domains" positive ($TIGIT^+$) T_{fh} cells has been observed[39, 96]. Given their central role in modulating immune responses, it is imperative to fully characterize the phenotype and function of the different T_{fh} subsets in individuals with SCA.

The major consequence of alloimmunization in SCA is the increase in risk for delayed hemolytic transfusion reactions (DHTR) upon subsequent blood transfusions[63, 97], which is an important cause of morbidity and mortality in individuals with SCA[97]. Management of alloimmunized individuals with SCA may also be complicated by difficulties in finding compatible blood which may cause delays in receiving transfusions[63]. Besides DHTR, alloimmunized individuals with SCA recipients of hematopoietic stem cell (HPSC) transplants were also found to have high rates of graft rejection[64, 65]. This is thought to be caused by sensitization to donor minor histocompatibility antigens during prior blood transfusions[64, 65, 98]. Overall, alloimmunization appears to significantly reduce survival in patients with SCA[99].

In mitigating the risk of alloimmunization brought about by repeated blood transfusions, several approaches including extended screening for rare antigens and leukoreduction of blood for transfusion have been proposed as effective measures[63, 81]. Immune therapy has also shown promise in treating complications of alloimmunization in individuals with SCA. Rituximab, an anti-CD20 antibody, has been successfully used to treat and prevent severe DHTR in patients with SCA[100, 101]. Antithymocyte globulin (ATG) has also been used with impressive results in reducing the incidence of HPSC transplant rejection among patients with SCA[102, 103]. It is imperative to continue to optimize these approaches, as well as advance elucidation of immune and non-immune mechanisms that protect select SCA patients against alloimmunization.

IMMUNE ACTIVATION IN SCA

SCA is increasingly recognized as a chronic inflammatory disease characterized by considerable immune activation[104, 105]. Immune activation is thought to contribute to the

pathogenesis of alloimmunization, transplant rejection and other inflammatory diseases in individuals with SCA.

The Spectrum and Sequelae of Immune Activation in SCA

The scope of immune activation in SCA is broad, involving cellular as well as humoral mechanisms. Besides neutrophil, monocyte, natural killer cell, platelet, mast cell and endothelial cell activation[106–111], evidence of lymphocyte activation has also been reported in SCA. Markers of lymphocyte activation reported in SCA include increased number of memory T cells[36, 37, 39], increased CD4+ and CD8+ T cell expression of Ki67[37] and increased T_{reg} expression of CTLA-4[25]. Augmentation of the pro-inflammatory Th17 response has also been observed in SCA[68], more so among recipients of multiple blood transfusions[30, 39] (Figure 1). Furthermore, patients with SCA have increased levels of C-reactive protein[31, 33, 112] and pro-inflammatory cytokines IL-6 and TNF-α[31, 32, 34, 35], and increased signaling through the pro-inflammatory Toll-like receptor 4, 7 and 8 (TLR4, TLR7 and TLR8) as well as through the inflammasome complex pathways[38, 40, 113, 114].

The state of immune activation is hypothesized to contribute to the pathophysiology of RBC alloimmunization[62, 63], and may also modulate immune responses to vaccines[115]. The risk for alloimmunization among SCA patients receiving blood transfusions is however is not uniform[63], suggesting role of genetic, immunologic and other factors in modification of alloimmunization risk[30, 39, 63, 96, 116, 117]. Most studies implicate a tipped balance towards increased inflammation through either impaired regulatory T cell (T_{reg}) and B cell (B_{reg}) activity, or enhanced pro-inflammatory environment with increased Th17 response and higher circulating levels of IL-6 and TNF-α as the underlying mechanisms that promote sensitization to allo-antigens in individuals with SCA[30, 39, 63, 116, 117]. Furthermore, TLR signaling was shown to enhance sensitization to allogeneic RBC antigens in mice[118, 119], although its contribution to RBC alloimmunization in individuals with SCA is yet to be determined. However, protracted immune activation has been associated with T cell exhaustion and impaired immune responses[120, 121], suggesting a balance between the degree and duration of immune activation in modulation of immunization risk. This delicate balance may explain the conundrum where both alloimmunization[63–65] and impaired responsiveness to vaccines[22, 41–43, 45] have been observed in individuals with SCA. Indeed, the risk of alloimmunization was found to be higher among SCA patients in the presence of inflammatory events such as acute chest syndrome, vaso-occlusive crisis and acute febrile illness at the time of transfusion[62], where circulating levels of the pro-inflammatory cytokines are high[34, 63]. On the other hand, impaired responsiveness to a yellow fever vaccine has been reported in an African population in the presence of immune activation[115], potentially due to immune cell exhaustion[115]. Infection with malaria has also been associated with lymphocyte activation[46, 47], and may thus augment inflammation among individuals with SCA living in malaria-endemic areas in sub-Saharan Africa[15]. Given the burden of infections in SCA, it is imperative to evaluate the impact of immune activation on vaccine responsiveness among individuals with SCA.

The incidence of systemic lupus erythromatosus (SLE) was found to be higher in individuals with SCA compared to that of the general population[66], concordant with an increase in titers

of anti-nuclear antibodies (ANA)[66]. Cases of rheumatoid arthritis have also been reported in SCA[122, 123], although no clear association of their occurrence with the level of immune activation in SCA has thus far been provided[122]. Thus, detailed elucidation of the pathogenesis of these inflammatory disorders in SCA is currently lacking. Part of the difficulties in studying these diseases in the setting of SCA is the salient similarity of their clinical presentations to that of the underlying SCA which may result in cases of SLE or rheumatoid arthritis being under-reported[123–125]. Whether development of SLE, rheumatoid arthritis and other inflammatory diseases in SCA is also linked to situational increases in levels of inflammation as observed with RBC alloimmunization[62] will be of interest to determine. Future studies should seek to further elucidate contribution of immune activation to the risk of inflammatory diseases in SCA.

Mitigating Immune Activation in SCA: Role of Hydroxyurea

Several approaches are currently being advanced as measures to mitigate the level of immune activation in SCA. Besides reducing the transfusion-induced alloimmunization risk via extended antigen screening and leukoreduction of blood for transfusion[63, 81], pharmacological agents have also shown benefits in reducing immune activation in patients with SCA. A notable example is hydroxycarbamide (hydroxyurea), which has been shown to confer beneficial reduction of immune activation in SCA. Specifically, the use of hydroxyurea has been shown to significantly overturn increased lymphocyte count, particularly circulating memory T cells, in individuals with SCA[37, 126]. This is postulated to occur via hydroxyurea-induced delay in G1 – S phase transition of naïve to memory T cell phenotypes through inhibition of ribonucleaotide reductase[126]. Hydroxyurea has also been shown to reduce TNF-α expression by lymphocytes and other immune cells[34, 35, 127], and is thought to reduce mast cell activation in individuals with SCA[108]. Importantly, hydroxyurea was generally found to be safe and well tolerated in children with SCA[128, 129], and did not increase risk of infections[129] or impair responsiveness to a pneumococcal vaccine[126], although a delay in responsiveness to a measles vaccine was observed[126]. Overall, immune changes due to hydroxyurea usage are thought to lead to beneficial normalization of the immune function and reversal of inflammation in SCA[34, 35, 37, 126, 127]. Indeed, in a randomized trial of hydroxyurea usage among patients with HIV on antiretroviral medication, the use of hydroxyurea resulted in the reduction of immune activation and improvement of HIV-specific CD4+ and CD8+ T cell responses[130]. As the usage of hydroxyurea is increasing in sub-Saharan Africa, more studies will be needed to assess its impact on immune function and vaccine reactivity in individuals with SCA.

Other inflammation-lowering strategies currently under investigation include the use of intravenous gammaglobulins, platelet adenosine diphosphate (ADP)-receptor blockers, adenosine A_{2A} receptor agonists and triterpenoids that have shown promise in reducing neutrophil activation, platelet activation, invariant natural killer T (iNKT) cell activation and oxidative stress, respectively, in patients with SCA[106, 107, 111, 131]. Further investigation of the benefits of these and other agents in managing immune activation in patients with SCA is warranted.

VACCINATION IN SCA

The goal of immunization in SCA is to elicit durable memory T and B cell responses that will help fight against infections, particularly due to encapsulated bacteria, especially during childhood. Currently, a number of vaccines have been licensed for use in individuals with SCA. These include vaccines against *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Neisseria meningitides*, hepatitis B and influenza[57, 132]. Since malaria in SCA is associated with high risk of mortality, the advent of a malaria vaccine will also help prevent deaths of children with SCA in malaria-endemic areas[14, 15, 17].

Studies on safety and immunogenicity indicate that most of the available vaccines, including pneumococcal, *Haemophilus influenzae* type B and influenza vaccines, are generally safe and immunogenic in children with SCA[133–141]. Indeed, the use of pneumococcal conjugate vaccines has substantially reduced the incidence of invasive pneumococcal disease in children with SCA[13, 142]. Nonetheless, incidences of impaired magnitude or duration of response to vaccines have been reported in individuals with SCA[26, 41–45]. In a study by Hord J *et al*, additional booster dose of the vaccine was required to optimize responsiveness to hepatitis B vaccine among individuals with SCA[43]. These observations potentially reflect the unique immune environment in individuals with SCA that may influence vaccine reactivity. To date, however, few randomized controlled trials of vaccines have been done among individuals with SCA, including only one trial of pneumococcal vaccine and none of *Haemophilus influenzae* type B vaccine[12, 20, 44]. Thus, recommendations for the use of these vaccines in SCA are based on efficacy trials done mostly in individuals without SCA[12, 18–20]. Although observational studies of the impact of pneumococcal conjugate vaccines in SCA have reported substantial reduction in invasive pneumococcal disease risk[13, 142], room still exists to improve vaccine outcomes even further to meet protection levels conferred among individuals without SCA[142]. Randomized controlled trials of these vaccines in SCA are therefore much needed, especially in sub-Saharan Africa where the burden of SCA is highest. Insights from these trials will inform optimization of vaccination and booster regimen required to improve the magnitude and duration of vaccine protection against infection in individuals with SCA[12].

Besides safety, immunogenicity and protective efficacy, coverage of pneumococcal vaccines against pneumococcal disease in SCA may be a challenge in sub-Saharan Africa. This is because of the highly diverse circulating pneumococcal serotypes in the region[143, 144]. Thus, although majority of the prevalent pneumococcal serotypes among children in sub-Saharan Africa are contained in the currently available pneumococcal conjugate vaccine - 10 and 13 (PCV-10, PCV-13)[61] and pneumococcal polysaccharide vaccine-23 (PPSV-23)[61], some prevalent serotypes including pneumococcal serotype 13 are not covered in the three vaccines[143, 144]. In settings where the proportion of circulating non-vaccine pneumococcal serotypes is high[143], dual usage of both the pneumococcal vaccines and penicillin prophylaxis is recommended and is considered complementary in individuals with SCA[9, 61, 145, 146]. A recent Cochrane review could not conclude when is safe to withdraw penicillin prophylaxis in children with SCA[9], but the American Academy of Pediatricians recommends continued use of penicillin prophylaxis at least until the age of 5 years[145, 146]. Prolonged use of penicillin prophylaxis beyond the age of 5 years may be recommended,

depending on the perceived risk of pneumococcal infection[61]. Penicillin resistance is varied, but may be high is select locations in sub-Saharan Africa[144, 147–149], and this may pose a challenge on the choice of regionally appropriate antibiotic to complement pneumococcal vaccination. Future studies should address both discovery of next generation pneumococcal conjugate vaccines with increased serotype coverage and identification of regionally appropriate antibiotics to complement pneumococcal vaccines in high penicillin resistance areas.

The schedules for the delivery of vaccines in individuals with SCA take into account the age of vaccine recipients and pathogen-specific infection risk in particular age groups[57, 58, 132]. For instance, the protein-conjugated PCV-10 and PCV-13, which elicit primarily T-cell dependent memory responses, are usually given during the first 2 years of life[58, 61]. The non-protein conjugated pneumococcal polysaccharide vaccine-23 (PPSV-23), which elicits T cell independent IgM memory B cell responses, is given to older individuals with mature spleen[57, 58, 61]. However, since splenic function is lost with age in individuals with SCA, this schedule should be modified in line with the recent recommendations for vaccination of individuals with hyposplenism[61]. Adaptation of the modified vaccine regimen must however be based on assessment of splenic function[58–61, 150], the capacity of which is currently lacking in most settings in sub-Saharan Africa. In view of the reported perturbations of lymphocyte phenotypes and functions in SCA, and accounts of impaired vaccine responsiveness in individuals with SCA, it is possible that differences in vaccine reactivity exists between patients with SCA compared to that in individuals without SCA. Furthermore, because of paucity of randomized controlled trials of vaccines in individuals with SCA, it is imperative to compare vaccines outcomes between individuals with and without SCA. The capacity to screen for hyposplenism should also be enhanced in resource limited settings, concurrent with increased research on its immune impact, in order to go hand in hand with the proposed recommendations for immunization of individuals with hyposplenism. Important areas for future research are summarized in Table 1 (Supplementary online information). Insights from these studies will inform optimization of the delivery of vaccines in individuals with SCA, including optimization of vaccination and booster schedules as may be needed, aiming at eliciting optimal and durable responses that will lead to reduction of the burden of morbidity and mortality due to infections in SCA.

CONCLUSIONS

It is clear that innate immune dysfunction is commonplace in SCA. Limited available evidence indicates that T and B cell functions are also compromised in individuals with SCA. Derangements reported include reduction in the proportion of circulating CD4+ and CD8+ T cells, reduction of CD4+ helper : CD8+ suppressor T cell ratio, a skewed Th2 response, dysfunction of regulatory T cells and loss of IgM-secreting CD27+$IgM^{high}IgD^{low}$ memory B cells, all occurring at the background of increased immune activation characterized by predominance of memory CD4+ T cell phenotypes, increased Th17 signaling and elevated levels of C-reactive protein and pro-inflammatory cytokines IL-6 and TNF-α. These abnormalities, and others uncovered, may affect vaccine reactivity in individuals with SCA. Since T and B lymphocytes are the primary cells for induction of vaccine-mediated immunity, it is imperative that their phenotypes and functions are

characterized in individuals with SCA. A comprehensive immunological and molecular analysis of T and B cells in SCA is therefore warranted, concurrent with detailed evaluation of the immunogenicity and protective efficacy of vaccines in individuals with SCA. This should include expanded analysis of responses of the different T and B cell subsets to infection and vaccination in SCA, together with assessment of their modulation by hyposplenism, splenectomy, genetic polymorphisms, alloimmunization, malaria endemicity and hydroxyurea usage. Studies should be encouraged of different SCA populations, including sub-Saharan Africa where the burden of SCA is highest. Insights from these studies will inform optimization of vaccination and booster schedules in order to overcome the burden of infections due to encapsulated bacteria and other pathogens in individuals SCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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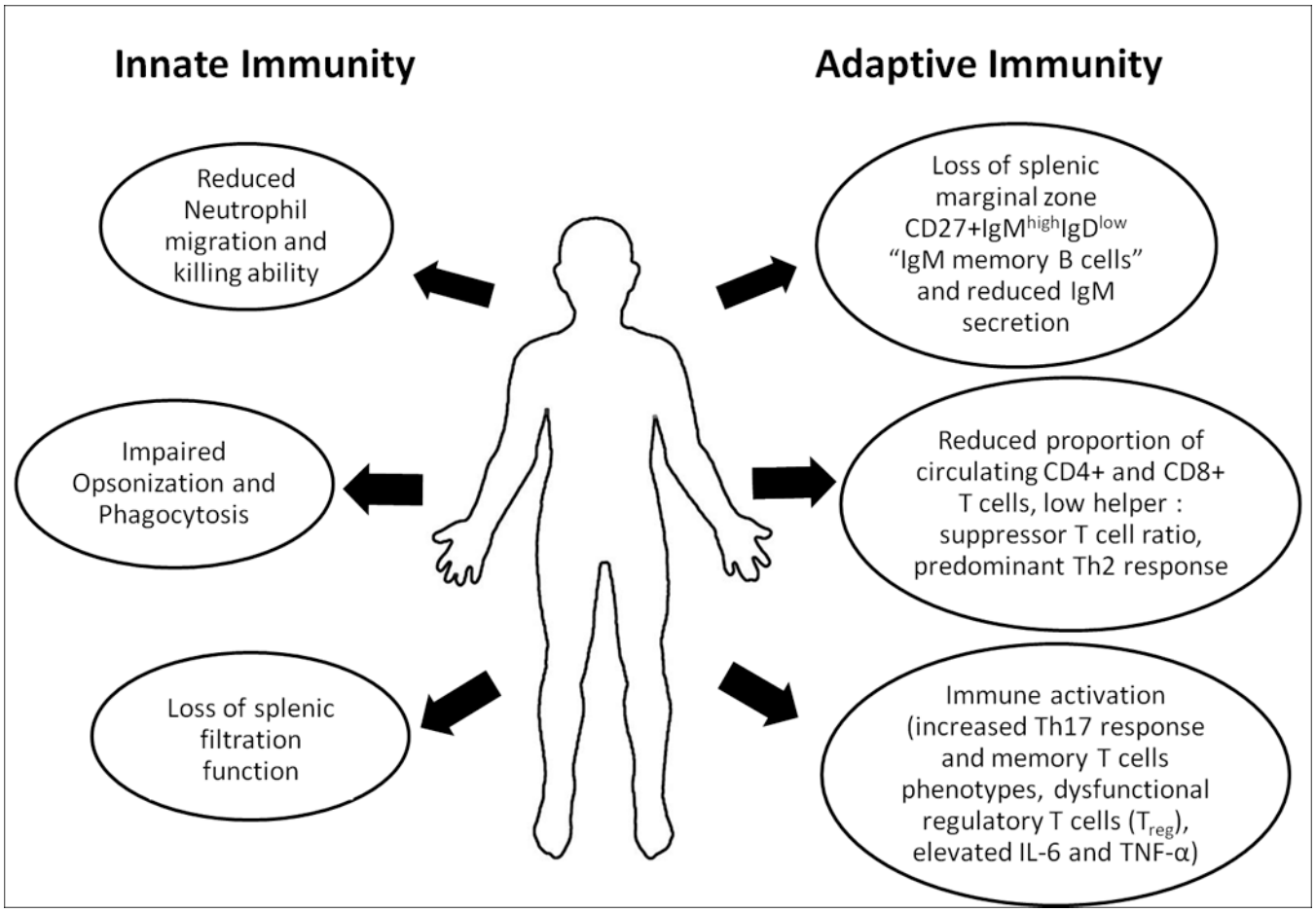

Figure 1.
Changes in innate and adaptive immune functions in sickle cell anemia.