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研究課題名（和文）Chronic impact of malaria on bone marrow niches and immune regulation after recovery from infection

研究課題名（英文）Chronic impact of malaria on bone marrow niches and immune regulation after recovery from infection

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　3,200,000円

研究成果の概要（和文）：骨髄における造血は、造血幹細胞（HSC）ニッチを形成する間葉系細胞からのシグナルによって調節されている。本研究では、マラリアが血管拡張を引き起こし、骨芽細胞を抑制し、骨髄の造血幹細胞ニッチ支持細胞の集団を減少させることを明らかにした。遺伝子トランスクリプトーム解析により、これらの造血幹細胞ニッチ支持細胞からのサイトカインがマラリア感染時に変化し、造血とリンパ球形成の障害につながることを明らかにした。このように、無症状の慢性マラリア感染が骨髄造血幹細胞ニッチに大きな障害を与えることが明らかになり、未診断の無症状症例が懸念される。

研究成果の学術的意義や社会的意義
This study reveals that infection such as malaria can modulate host immune responses by affecting bone marrow hematopoiesis through the alteration of bone marrow niches. This study suggests that malaria may have chronic impact on host immunity.

研究成果の概要（英文）：Hematopoiesis in the bone marrow is modulated by signals from mesenchymal cells that form the hematopoietic stem cell (HSC) niches. In this study, we found that malaria causes vasodilation, inhibits osteoblasts, and reduces a population of HSC niche supporting cells in the bone marrow. Gene transcriptomic analysis revealed that cytokines from these HSC niche supporting cells altered during malaria infection which led to impaired hematopoiesis and lymphopoiesis. We found that chronic asymptomatic malaria infection had a profound damage on bone marrow hematopoietic niches, raises the concern of asymptomatic cases that remain undiagnosed.

研究分野：マラリア免疫学

キーワード：Malaria　Bone marrow　Hematopoiesis

１．研究開始当初の背景

Over 200 million cases of clinical malaria were reported annually (WHO, 2022). Nearly half of the world's population is still at risk of malaria due to the rise of antimalarial drug resistance, challenges in blocking mosquito transmission of *Plasmodium* parasites, and the under reported cases of persistent asymptomatic malaria serves as reservoir for sustained transmission (Topazian HM, 2020). It has been reported that past record of malaria infection could leave some survivors to suffer from neurological deficit and increased susceptibility to other diseases (Lee MSJ et al., 2018). Reduction in malaria infection cases often results in total reduction in all-cause morbidity, suggesting the negative impact of malaria on host immunity (Chen I et al., 2016). Immune evasion by malaria renders great challenge in malaria vaccine development, and this may not limit to the case of malaria alone, but also may contribute to compromised immunity to other infection and vaccination.

We reported that the long-term accumulation of *Plasmodium* parasite products in the bone marrow after recovery from malaria infection could eventually lead to bone loss (Lee MSJ et al., 2017) (Figures 1 and 2). This suggests that malaria causes dysregulation of crosstalk between immune and bone systems in the bone marrow.

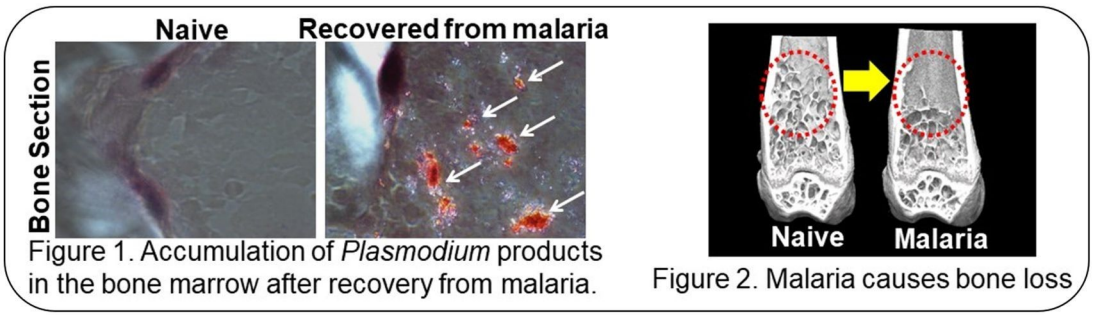

Figure 1. Accumulation of *Plasmodium* products in the bone marrow after recovery from malaria.

Figure 2. Malaria causes bone loss

Bone marrow is the house of hematopoietic stem cells that give rise to most immune cells. Development of hematopoietic stem cells is supported by microenvironmental niches in the bone marrow created by various mesenchymal stromal cells and vasculature (Sugiyama T et al., 2018). These niches provide signals such as chemokine, cytokine and growth factors for immune cell regulation and memory cell maintenance in the bone marrow (Nagasawa T, 2006). Bone marrow stromal cells are very sensitive to stressors such as infections and can affect hematopoiesis and host immunity (Nombela-Arrieta C et al., 2017).

Key scientific questions:

- Does malaria infection alter bone marrow niches and subsequently affect the cellular distribution, differentiation, and function of immune cells?

２．研究の目的

This study aims to evaluate the acute and chronic effects of different malaria models on bone marrow microenvironment, cell populations and spatial distribution of bone marrow niches. This study further aims to examine the effects of malaria on differentiation potential and cellular function of bone marrow cells.

３．研究の方法

To evaluate the acute and chronic effects of malaria on bone marrow cell population, we infected the mice with three different *Plasmodium* parasites that cause different malaria pathology. *P. berghei* ANKA infection model causes acute severe malaria that resembles nonimmune individual who get malaria. *P. yoelii* Non-Lethal infection model causes acute uncomplicated malaria that is self-resolving. *P. chabaudii* infection model mimics chronic asymptomatic infection in malaria endemic region as a result of partial immunity developed from an acute uncomplicated infection. To examine the changes of bone marrow cell populations during malaria infection and recovery, bone marrow cells were isolated from malaria infected mice, recovered mice, and control naïve mice for flow cytometry analysis. Subsets of hematopoietic stem and progenitor cells, multipotent progenitors, immune cell subsets at different developmental stages and activation states were examined. Subsets of mesenchymal stem cells that make up the hematopoietic stem cell niches were also isolated and analyzed by flow cytometry. Effect of malaria on gene expressions of cytokine, chemokines and growth factors that modulate hematopoietic stem cell maintenance and differentiation were analyzed by quantitative PCR. To examine the structural changes and spatial distribution of cells within the bone marrow caused by malaria, immunohistochemical staining and 3D bone staining were optimized for confocal microscopy analysis.

４．研究成果

This study reveals that acute malaria caused by three different *Plasmodium spp.* infections consistently led to increased hematopoiesis, and a bias in HSC differentiation potential. We found that the suppression of some populations in the bone marrow was associated with the changes in the bone marrow niches. We found that acute malaria consistently led to depletion of a major hematopoietic stem cell (HSC) niche-supporting cell population within the bone

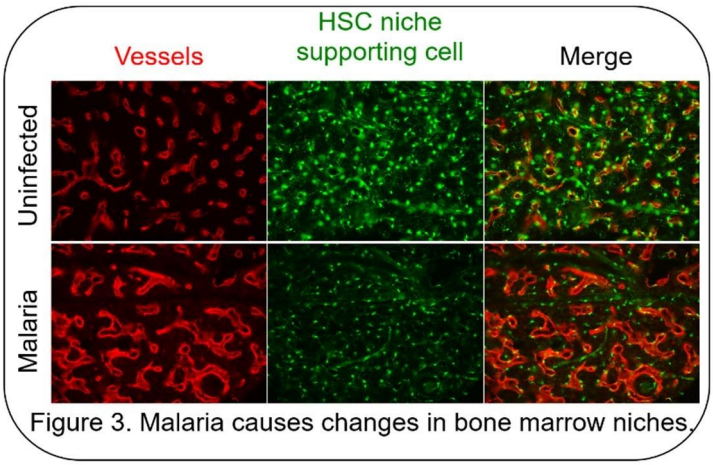

Figure 3. Malaria causes changes in bone marrow niches.

marrow (Figure 3). This phenotype was also observed in low chronic asymptomatic malaria caused by *P. chabaudi* infection when parasites were not detectable in the blood. This observation was consistent in flow cytometry analysis and by microscopy analysis. Further transcriptomic analysis showed that some chemokine and cytokines secreted by this population of HSC niche supporting cell were altered by malaria infection. We successfully optimize the method for high resolution 3D microscopy imaging of bone marrow that retains the cellular integrity and distribution. We found that bone marrow vessels surrounded by this population of HSC niche supporting cells were observed to be dilated during acute infection by confocal 3D microscopy imaging. Further studies are on-going to evaluate the impact of the alteration of bone marrow microenvironment on the host immunity and the underlying mechanisms.

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５．主な発表論文等

〔雑誌論文〕　計1件（うち査読付論文　1件／うち国際共著　1件／うちオープンアクセス　1件）

１．著者名 Lee Michelle S.J.、Inoue Takeshi、Ise Wataru、Matsuo-Dapaah Julia、Wing James B.、Temizoz Burcu、Kobiyama Kouji、Hayashi Tomoya、Patil Ashwini、Sakaguchi Shimon、Simon A. Katharina、Bezbradica Jelena S.、Nagatoishi Satoru、Tsumoto Kouhei、Inoue Jun-Ichiro、Akira Shizuo、Kurosaki Tomohiro、Ishii Ken J.、Coban Cevayir	４．巻 219
２．論文標題 B cell-intrinsic TBK1 is essential for germinal center formation during infection and vaccination in mice	５．発行年 2021年
３．雑誌名 Journal of Experimental Medicine	６．最初と最後の頁 e20211336
掲載論文のDOI（デジタルオブジェクト識別子） 10.1084/jem.20211336	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

〔学会発表〕　計2件（うち招待講演　0件／うち国際学会　0件）

１．発表者名 LEE Michelle Sue Jann
２．発表標題 Effects of malaria on bone marrow hematopoietic stem cell niches
３．学会等名 第51回日本免疫学会学
４．発表年 2022年

１．発表者名 LEE Michelle Sue Jann
２．発表標題 Effects of malaria on bone marrow hematopoietic stem cell niches
３．学会等名 第15回寄生虫感染免疫研究会
４．発表年 2023年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関