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科学研究費助成事業　　研究成果報告書

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研究課題名（和文）マラリア感染における脳内免疫反応の4次元イメージング

研究課題名（英文）4D imaging of brain and the immune system during cerebral malaria

研究代表者

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研究成果の概要（和文）：血液脳関門（Blood-Brain Barrier, BBB）の機能障害は脳マラリアの主症状であるが、それがどのように起きているかほとんどわかっていない。私たちは超高磁場MRIおよび多光子顕微鏡を用いて嗅球が器質的および機能的にマラリア原虫によって損傷を受けていることを示した。嗅球を形成する索状微小毛管において、高熱とサイトカインストームに関連した、微小出血による寄生原虫の集積と細胞閉塞等が見られる。嗅覚喪失の早期検知と病原細胞の集積阻害による脳マラリアの初期段階での治療への応用が考えられる。

研究成果の概要（英文）：The dysfunction of BBB is the main feature of cerebral malaria; however, little is known how it occurs. We have shown by ultra-high field MRI and multiphoton microscopy that the olfactory bulb is physically and functionally damaged by Plasmodium parasites. The trabecular small capillaries comprising the olfactory bulb show parasite accumulation and cell occlusion followed by microbleeding, events associated with high fever and cytokine storm. Early detection of olfaction loss and blockade of pathological cell recruitment may offer potential therapeutic strategies.

研究分野：　寄生虫学(含衛生動物学)

キーワード：　感染症　　免疫学　　マラリア　　Olfactory Bulb　　Plasmodium bergheiANKA

科学研究費助成事業　研究成果報告書

１．研究開始当初の背景

The dysfunction of the blood-brain-barrier (BBB) is the main feature of various central nervous system inflammatory disorders including cerebral malaria (CM); however, little is known how it occurs. Evidences suggest that there is a “cross-talk” between brain and immune system. In this study, we aimed to elaborate immune cells dynamics causing BBB leakage and cerebral malaria by a new approach, bringing together immunology, neuroscience and imaging technologies.

２．研究の目的

Blood-brain barrier is believed to be a key player to control trafficking of cells to the brain. The dysregulation of the BBB could be the most common key feature for various neurological inflammatory disorders as diverse as multiple sclerosis and cerebral malaria. To comprehensively investigate cross-talk between brain and the immune system during CM, one of the powerful approaches is to use highly advanced imaging techniques such as magnetic resonance imaging (MRI, 11.7 T) and/or two-photon microscopy brain imaging. Advanced whole brain non-invasive MRI imaging offers new and fast diagnosis of CM. Two-photon live imaging provides advantages for studying single-cell dynamics in tissue explants and living mice that offers to observe the dynamics of immune cells in detail during CM. Thus, our purpose was to elaborate pathology of CM by combining these cutting-edge technologies.

３．研究の方法

1. Non-invasive imaging of brain during CM by 11.7T MRI. In collaboration with Prof Yoshioka of IFReC, Osaka University, we extensively visualized CM brain by ultra-high-field MRI to understand which parts of brain is the most affected by parasites.

2. Investigation of the inflammatory cells which play important role in the pathogenesis of CM; The CD8+ T cells have been known to migrate and responsible for the pathology of CM. Together with parasites, how and in which order these cells migrate into brain has not been fully addressed. By using multiphoton microscope, we investigated how CD8 T cells and parasites interact in brain.

3. Investigation of cause and result of immunological events occurring in olfactory bulb during CM by immunological methods such as IHC and FACS analysis.

４．研究成果

1. We have identified in mice that the olfactory region is a vulnerable location for vascular leakage during experimental cerebral malaria in which this discovery, a physical disruption of olfactory bulb, could only be possible by using an ultra-high field MRI.

2. By using simple assay, a buried-food assay, olfactory bulb was also found to be damaged functionally (loss of smell) by Plasmodium parasites. In addition, this event is followed by high fever. Thus, we identified that there is an early symptom, olfaction loss, before the onset of coma.

3. We confirmed MRI findings with multiphoton live imaging that olfactory bulb is a very unique organ with special architectural structure, therefore, olfactory easily undergoes parasite accumulation and cell occlusion followed by micro-bleeding.

4. Additional immunohistochemistry analysis showed that circulating parasites in the olfactory vessels are sensed by astrocytes around olfactory glomeruli at the early stage of infection, and may release CCL21 and may have a role for the recruitment of pathological CD8 T cells into brain.

5. We further evaluated this novel understanding into a novel intervention strategy by blocking chemokine-receptor interactions when the early symptom of experimental cerebral malaria, olfaction loss, was evident. Functional blockade of the CCL21 receptors CCR7 and CXCR3 respectively results in decreased CD8 T cell activation and recruitment as well as prolonged survival.

6. Given that even 1 day early detection of malarial coma could increase treatment success dramatically; this previously unnoticed, truly overlooked location and detection of olfaction loss during malaria infection may provide early, cheap and easy diagnosis of cerebral malaria.

５．主な発表論文等
（研究代表者、研究分担者及び連携研究者には下線）

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〔図書〕（計　0 件）

〔産業財産権〕
○出願状況（計　1 件）
名称：Diagnosis and medical treatment for cerebral malaria
発明者：C. Coban, Y. Yoshioka, T. Aoshi, K.J. Ishii
権利者：Osaka University/NIBIOHN
種類：Application
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国内外の別：Overseas

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取得年月日：
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〔その他〕
ホームページ等

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http://www.ifrec.osaka-u.ac.jp/en/research/20140515-0701.htm

http://resou.osaka-u.ac.jp/ja/research/2014/20140515_1

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