様式３

論　文　内　容　の　要　旨

氏　名　（　陳 挺　）	
論文題名	ナノ磁性粒子を用いた超高磁場MRI新規生体機能イメージング法の開発

Nowadays, MRI contrast agent plays an indispensable role not only in clinical diagnostics but also in the bioscience research, because of their ability to aid discrimination by enhancing specific features. Over the last decades, numerous attempts have been made to improve the sensitivity and specificity of contrast agent using different techniques to achieve better image contrast continuously. The primary research object of the paper is about a new super paramagnetic iron oxide (new SPIO) nanoparticles as one kind of MRI contrast agents, which have concentrated polymer brushes in the outer shell and are difficult for phagocytes to absorb. The principal aim of this study was to investigate the biodistribution and retention properties of this new SPIO, and also aimed to verify the possibility of this new SPIO to be used as a new biofunctional imaging method to assess organs function by using kinds of disease mouse models of nephritis and multiple sclerosis in ultra-high field MRI system.

Firstly, I investigated the biodistribution and retention properties of new SPIO in normal mouse, and to compare the new SPIO with clinically approved SPIO (Resovist). I found that the contrast pattern of new SPIO is quite different from Resovist, especially in the kidney of mouse, new SPIO exhibited a unique MRI contrast pattern which can not observed with other contrast agents. And the results of TEM showed that numerous of new SPIO particles were engulfed by mesangial cells in kidney glomeruli, even though the new SPIO was absorbed in only negligible amounts by phagocytes in liver and lymphatic tissues due to its stealth. These results indicate that the new SPIO may be potentially be used as a new contrast agent for the assessment of kidney function because mesangial cells play important roles in renal physiology and immune function.

Secondly, I verified the possibility of this new SPIO to be used as a new contrast agent for the assessment of kidney function by using a kind of IgA nephritis mouse model, due that new SPIO particles were engulfed by mesangial cells in glomeruli and exhibited a unique MRI contrast pattern in normal mouse kidney. And I also compared the new SPIO with Resovist in this study. I found that new SPIO didn't show any contrast effect in the kidney of nephritis mouse model, which is quite different from that in normal mouse. However, the Resovist did not show any difference in the kidneys between the normal mouse and IgA nephritis mouse model. These results indicate that Resovist and the new SPIO have an entirely different mechanism of accumulation in glomeruli. I also verified that the new SPIO can be used as a new approach to the assessment of kidney function due that the contrast effect changes when inflammation occurred in glomeruli.

Thirdly, I combined the anti-Smith (anti-Sm) antibody which is a specific marker for SLE to the new SPIO, aimed to synthetize a new particle with more sensitivity and specificity. And used this antibody combined particle into SLE model mice to investigate whether this new particles show the specific distribution and retention properties in the kidneys. The MRI images revealed that the antibody combined particle shows a specific distribution and long retention time in the cortex of the kidney in lupus nephritis mouse model, but not in wild type WT mice. These results suggest that the distribution pattern of this new particle in the renal corpuscle may reflect the symptoms of kidney disease in lupus nephritis mouse models, and it also shows the potential for use as a molecular-targeted imaging agent to assess the lupus nephritis in vivo.

The first study's results showed that the new SPIO didn't show contrast effect in normal mouse brain because of its stealth property and the existence of blood -brain barrier (BBB). Therefore, I speculated that the new SPIO would exhibit a different contrast pattern in the brain when BBB was breakdown, and could be used for the assessment of BBB as a new approach. In the last study I investigated the usability of new SPIO to assess the damage of BBB in a multiple sclerosis mouse model (EAE), and also evaluated the activity of immune cells in different stages of EAE model mouse by using the Resovist. I found that the new SPIO showed a specific distribution in the brain and spinal cord which corresponding to the ruptured BBB of onset mouse, but not in the recovery model and the normal mice. And the Resovist showed different contrast effect in the different stage which is corresponding to the dynamics change of cellular immunity. I also found that new SPIO group's results showed us that there is a time different on the rupture and recovery of BBB between the brain and spinal cord in EAE model from the MRI results of new SPIO groups. These results suggest that the possibility of a new imaging method using a combination of new SPIO and Resovist, which could make a contribution to the research on the pathogenesis of EAE.

In this study, I have developed some new applications for the new SPIO and Resovist, and successfully got the unique MRI contrast patterns which could not obtained by other contrast agents. The results suggest that they can be used as a new biofunctional imaging method to assess the organs function, and make a contribution to the bioscience research.

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論文審査の結果の要旨及び担当者

氏　名（　陳 挺　）		
	（職）	氏　名
論文審査担当者		
主 査	教授	吉岡　芳親
副 査	教授	高島　成二
副 査	教授	八木　　健

論文審査の結果の要旨

本論文では、高感度で高精細な画像が得られる超高磁場MRI装置を用い、更に、MRI造影剤として、高磁場環境でより有効なナノ磁性粒子を用いる事で、詳細なイメージングができることを示した。具体的には、11.7Tの小動物用超高磁場MRI装置を用いて、健常や病態モデルマウスを対象とし、ヒト臨床での使用が認められてきたナノ磁性粒子（Resovist）と共同研究者により新たに作られたいくつかのナノ磁性粒子（新規磁性粒子）を用いて、新たなイメージングに挑戦し成果を生み出した。新規磁性粒子では、マクロファージなどの貪食細胞に貪食されにくいステルス性の磁性粒子に特に注目し研究を進めた。このステルス性ナノ磁性粒子は、臨床で用いられてきたResovistとは異なり、投与後には肝臓やリンパ系組織には殆ど分布しないが、他のいくつかの臓器では特異的な分布を示すことを明らかにした。特に、腎臓においてユニークな分布を示すことを発見し、さらに、このステルス性ナノ磁性粒子が健常時には糸球体のメサンギウム細胞に取り込まれることを明らかにした。これは、メサンギウム細胞がマクロファージやクッパー細胞などの貪食細胞が認識しない粒子を認識し取り込むことを示しており、非常に重要な発見だと思われるし、論文では、さらに、ステルス性ナノ磁性粒子が腎機能や腎疾患の評価にも応用できることも示した。中枢神経系の難病である多発性硬化症のモデルマウスにも上記磁性粒子を活用し、病態の進行・寛解に伴う脳血液関門の破綻と免疫細胞の関与を時系列で区別して可視化できることも示した。

申請者の研究成果は、1報が既にMRIの専門誌に発表できており、執筆中の論文が2報である。国際学会や国内学会でも次々と発表できており、2015年の第43回日本磁気共鳴医学会大会では最優秀大会長賞を受賞（3名のみが受賞）した。2017年の国際磁気共鳴医学会日本支部学術集会では優秀発表賞を受賞（4名のみが受賞）した。腎炎に関係した研究成果の一部は、特許申請し、現在、特許審査中である。

申請者の以上の研究成果は、申請者のMRI・動物実験・病態モデル動物に関する知識とともに、実験技術や解析能力を含めた研究能力の高さを示すものであり、博士号を授与されるに値すると判断した。