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研究課題名（和文）Uncovering a novel therapeutic target for BMT-induced inflammation

研究課題名（英文）Uncovering a novel therapeutic target for BMT-induced inflammation

研究代表者
劉　知昇（Yoo, Ji-Seung）

北海道大学・医学研究院・助教

研究者番号：３０８４３４３７

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研究成果の概要（和文）：移植片対宿種病（GVHD）は同種造血幹細胞移植の望ましくない副作用であり、白血病患者の治療に当たっては多大なる制限となりうることがある。しかしながら、未だその効果的な治療は未開発である。本研究ではGVHDを発症させる分子標的を特定することが目的であり、MHCクラスI分子に焦点を当てた結果、MHCクラスI分子の転写因子であるNLRC5分子がGVHD発症に非常に重要な役割を補っていることを発見した。さらに、マウスモデルを使用したNLRC5分子の枯渇化実験に関しては、将来のGVHD治療開発にあたり非常に有利なアイデアであることを見出した。

研究成果の学術的意義や社会的意義
Organ transplantation recipients develop severe GVHD. However, current treatments are limited with strong side effects. More importantly, those drugs do not fundamentally cure the disease. My study contributes to the current science field and society by providing a novel therapeutic target for GVHD.

研究成果の概要（英文）：Graft-versus-host disease (GVHD) is an unfavorable side effect of the allo-HSCT and a major limitation for the treatment of leukemia patients. However, currently, there are no effective medications available. The goal of my project was 1) to understand the underlying mechanism of the development of GVHD, 2) identify a molecular target involved in the disease onset, and 3) develop a novel therapeutic approach. During 2 years, I focused on the MHC class I pathway that is critically associated with disease onset and pathogenesis and achieved my research goals. I clarified that NLRC5, a master transactivator of the MHC class I pathway plays a critical role in the GVHD pathogenesis. Depletion of NLRC5 genes using the mouse model showed improved clinical outcomes. These findings will provide a novel idea for the development of GVHD therapeutics.

研究分野：Immunology. Inflammatory and iInfectious disease.

キーワード：GVHD　MHC class I　NLRC5　Molecular target　Therapeutics

１．研究開始当初の背景

Graft-versus-host disease (GVHD) is an unfavorable side effect of the allo-HSCT and a major limitation for the treatment of leukemia patients. Critically, 15% to 20% of stem cell transplantation recipients develop severe GVHD that is refractory to therapy and account for death. Current treatments for GVHD rely on the broad suppression of T cell activation and inflammatory responses with calcineurin inhibitors and corticosteroid. However, those immunosuppressive agents and steroids have strong side effects and do not fundamentally cure the pathogenesis of the disease. Thus, the prevention and treatment of GVHD remains a major challenge and required to be improved.

２．研究の目的

The goal of my project was 1) to understand the underlying mechanism of the development of GVHD, 2) identify a molecular target involved in the disease onset, and 3) develop a novel therapeutic approach. To achieve the research goals, I focused on the MHC class I pathway that is critically associated with disease onset and pathogenesis. Identification of the critical molecular factor(s) that is tightly associated with an organ transplantation-induced MHC class I pathway will be a molecular target for the development of novel GVHD therapeutics.

３．研究の方法

Recent studies have been shown the involvement of MHC class I in the pathogenesis of GVHD. Thus, we analyzed the mechanistic aspect of the onset of GVHD induced by activation of the MHC class I pathway using both in vitro and in vivo knockout mouse system.

４．研究成果

Using *in vivo* knockout mouse system, we found that activation of the MHC class I expression positively correlates with pro-inflammatory cytokine production and tissue damage in mouse

GVHD model. My studies demonstrated that: (1) Expression of MHC class I is induced in GVHD target organs in a mouse model of bone marrow transplantation (BMT), and inflammatory cytokine expression level is correlated, (2) a significant decrease of inflammatory cytokine production and $CD8^+$ T cell proliferation, and (3) reduced GVHD target tissue damage in the reduced MHC class I pathway. Thus, these findings may provide a novel therapeutic target for the GVHD treatment.

- **Disclosure note:**

  Since this project is currently being prepared for the patent application, here I show limited information from the study. Thus, data is not shown in this report.

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 Kasuga Yusuke、Zhu Baohui、Jang Kyoung-Jin、Yoo Ji-Seung	４．巻 .
２．論文標題 Innate immune sensing of coronavirus and viral evasion strategies	５．発行年 2021年
３．雑誌名 Experimental & Molecular Medicine	６．最初と最後の頁 .
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/s12276-021-00602-1	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1件（うち招待講演　0件／うち国際学会　0件）

１．発表者名 JI-SEUNG YOO
２．発表標題 The Molecular Mechanism Governing the Expression of NLRC5, a Mastery Regulator of MHC Class I Pathway
３．学会等名 日本免疫学会
４．発表年 2019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