様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　５ 年　 ５ 月 ２９ 日現在

機関番号：１０１０１
研究種目：基盤研究(C)（一般）
研究期間：2020～2022
課題番号：２０Ｋ０７４２０

研究課題名（和文）縦隔関連リンパ組織に着目したヒト呼吸器・心血管疾患の革新的な治療戦略研究

研究課題名（英文）innovative therapeutic approach of some devasting respiratory and cardiac diseases via MFALCs targetting

研究代表者
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研究者番号：３０７８２２２１

交付決定額（研究期間全体）：（直接経費）　　3,300,000円

研究成果の概要（和文）：糖尿病や肺喘息における縦隔関連リンパ組織（ MFALCs）の発達の程度や病的な肺障害を明らかにした（Elewa et al. 2021, Micros Microanal Int.; 2021 J. Mol. Sci.）。また、自己免疫誘発肺病変におけるMFALCsの発生と肺傷害に対するデキサメタゾンまたはブレオマイシンのいずれかの影響を報告した（Elewa et al. Front. Immunol. 2021; Micros Microanal 2022; Int. J. Mol. Sci.2022）。また、30篇以上の共著論文を公表した。

研究成果の学術的意義や社会的意義
We clarified the impact of MFALCs targeting in the revealing of lung injury in several mice models. Therefore, this study could open the bright future of human respiratory diseases by introducing innovative therapeutic strategies for respiratory diseases

研究成果の概要（英文）：The pathological Alternations of mediastinal fat-associated lymphoid clusters (MFALCs) and lung injury following metabolic disorder (diabetes induction) (Elewa et al. 2021, Microscopy and microanalysis) and asthma induction (Elewa et al. 2021, Int. J. Mol. Sci.) were revealed. Furthermore, we could clarify the impact of either dexamethasone or bleomycin on the degree of lung injury and MFALCs development in autoimmune-induced lung lesions. From the data analysis of these experiments, I could publish in three high-impact Journals (Elewa et al. 2021, Front. Immunol.; Elewa et al. 2022, Microscopy and Microanalysis; Elewa et al. 2022, Int. J. Mol. Sci.). Also, through collaborative research with other researchers within my lab and other institutions inside Japan and outside Japan, and from this collaboration, I could publish the data in 30 high impacted Journals.

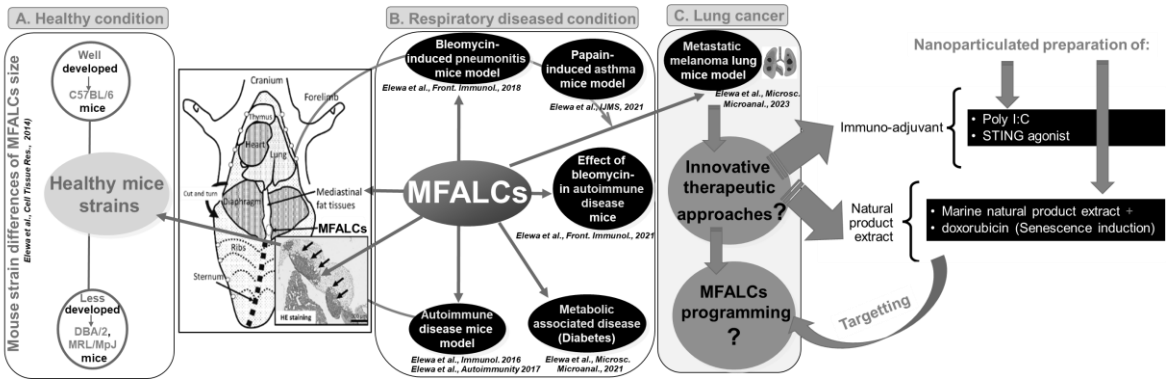
研究分野：Immunity and lung lesions

キーワード：lung injury　MFALCs　streptozoticin　Lung asthma　diabetes　Bleomycin　autoimmune diseases　immune cells

１．研究開始当初の背景

Mediastinal fat-associated lymphoid clusters (MFALCs) are novel lymphoid clusters that I discovered to be associated with the mediastinal adipose tissue in the chest and characterized by their unique content of innate lymphoid cells (natural helper cells) of that play an important role in the pathogenesis of many chest cavity diseases (Elewa et al., *Cell Tissue Res* 2014). Our previous reports revealed a correlation between MFALCs development and the pathogenesis of lung injury using several (including genetic autoimmune disease mouse models (Elewa et al., *Immunol.* 2016; *autoimmunity* 2017); aseptic conditions such as bleomycin induced-pneumonitis mouse model (Elewa et al., *Front. Immunol.* 2018); septic condition such as *Mycoplasma pulmonis* infection in mice (Boonyarattanasoonthorn et al., *Infection, Genetics, and Evolution* 2019). My data suggests a potentially important role for MFALCs in the intrapleural environment, but their functional role in the pathogenesis of respiratory diseases that requires innovative strategies for their treatment such as lung asthma and lung cancer remain unclear. Furthermore, the impact of anti-inflammatory medication on the amelioration of lung lesions via targeting MFALCs in autoimmune mice models is not yet clarified. Therefore, I suggested that such clusters could play an important role in the progression of chronic respiratory diseases via the crosstalk with MFALCs immune cells. Furthermore, targeting MFALCs inactivation in autoimmune diseases could improve lung injury. Therefore, further investigations are required to examine our hypothesis (Fig. 1).

Fig. 1: Role of MFALCs in the pathogenesis of lung injury and disease recovery



２．研究の目的

Our investigation aims to elucidate the functional contribution of MFALCs in the pathogenesis of chronic respiratory diseases using mice models. Additionally, our aim is to clarify if targeting MFALCs regression in autoimmune diseases could contribute to the amelioration of lung injury. Moreover, our study aimed to examine the pathological contribution of MFALCs and their role in lung cancer progression in the metastatic lung melanoma mice model. Therefore, our study could present cutting-edge research in innate immunity that could help to update FALCs immunity and clarify the pathogenesis of several respiratory diseases that require innovative therapeutic approaches.

３．研究の方法

Various mouse models for respiratory diseases were induced and examined in this study to clarify what kind of diseases could alter MFALCs. Such mouse models include aseptic lung asthma mice models (e.g. following intranasal administration of

papain), and genetic autoimmune disease mice models. Also, we examined the ameliorative effect of dexamethasone and the impact of bleomycin on the development of MFALCs and lung injury in autoimmune disease models. Additionally, a lung cancer mice model was induced. And immune cells in the MFALCs and within the vicinity of lung cancer were analyzed in early and late stages to characterize the microenvironmental changes in both early and late lung cancer. Histopathological examination including immunohistochemical analysis and gene expression of MFALCs and lung, and immune characterization in MFALCs are compared between control and diseased groups. Furthermore, pathological correlations between lung pathological scores (e.g. immune cell infiltration, alveolar structures) and MFALC structural changes (e.g. size, cell population) are clarified. Furthermore, a histomorphometric and immunological investigation was performed on the mesentery and chicken air sacs of chicken for the occurrence of lymphoid clusters in association with the adipose tissue.

４．研究成果

Through our study, we could address the following points (Fig. 1):
- Possible crosstalk of the immune cells within the lung and MFALCs in the acute inflammatory lung asthma-like mouse model following intranasal administration of papain (Elewa et al, Int. J. Mol. Sci. 2021).
- Dual effect of bleomycin on histopathological features of lungs and mediastinal fat-associated lymphoid clusters in an autoimmune disease mouse model (Elewa et al., Front. Immunol. 2021). We also revealed the histopathological impact of bleomycin on lung injury and the development of MFALCs in the lymphoproliferative mouse model (Elewa et al, Microscopy and Microanalysis 2022).
- The ameliorative effect of dexamethasone on the autoimmune disease lung injury via targeting the regression of MFALCs (Elewa et al., Front. Immunol. 2022).
- Additionally, we revealed the microenvironmental changes of MFALCs and lungs in the early and late stages of metastatic lung melanoma induction (Elewa et al. Microscopy and Microanalysis 2023).
- Furthermore, through our histopathological examination of the chicken air sacs and mesentery, we could report a novel immunological role through the localization of lymphoid clusters (Elewa et al. Microscopy and Microanalysis 2023).
- Also, through collaborative research on lumpy skin disease in cattle, we could characterize the cellular infiltration, cytokines, and histopathology of skin lesions associated with different clinical forms and stages of the disease (Elewa et al. Comparative Immunology, Microbiology, and Infectious Diseases 2022).

５．主な発表論文等

〔雑誌論文〕　計10件（うち査読付論文　5件／うち国際共著　5件／うちオープンアクセス　5件）

１．著者名 Yaser H A Elewa, Mahmoud Abd Elwakil, Osamu Ichii , Teppei Nakamura , Sherif Kh A Mohamed, Yasuhiro Kon	４．巻 22 (6878)
２．論文標題 Possible Crosstalk of the Immune Cells within the Lung and Mediastinal Fat-Associated Lymphoid Clusters in the Acute Inflammatory Lung Asthma-Like Mouse Model	５．発行年 2021年
３．雑誌名 Int J Mol Sci .	６．最初と最後の頁 1-18
掲載論文のDOI（デジタルオブジェクト識別子） 10.3390/ijms22136878	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

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２．論文標題 Dual Effect of Bleomycin on Histopathological Features of Lungs and Mediastinal Fat-Associated Lymphoid Clusters in an Autoimmune Disease Mouse Model	５．発行年 2021年
３．雑誌名 Front Immunol .	６．最初と最後の頁 1-17
掲載論文のDOI（デジタルオブジェクト識別子） 10.3389/fimmu.2021.665100	査読の有無 有
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掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.biopha.2021.112029	査読の有無 有
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１．著者名 El-naseery N.I., Elewa Y.H.A., Arafa M.A.A., Sabbah W.S., Dessouky A.A	４．巻 263: 151714
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３．雑誌名 ANNALS OF ANATOMY-ANATOMISCHER ANZEIGER	６．最初と最後の頁 1-9
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.aanat.2021.151714	査読の有無 有
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2．論文標題 Osteoblast-activating peptide exhibits a specific distribution pattern in mouse ovary and may regulate ovarian steroids and local calcium levels	5．発行年 2021年
3．雑誌名 Am J Transl Res	6．最初と最後の頁 5796-5814
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1．著者名 Elewa Yaser H.A.、Ichii Osamu、Nakamura Teppei、Kon Yasuhiro	4．巻 27
2．論文標題 Pathological Alternations of Mediastinal Fat-Associated Lymphoid Cluster and Lung in a Streptozotocin-Induced Diabetic Mouse Model	5．発行年 2020年
3．雑誌名 Microscopy and Microanalysis	6．最初と最後の頁 187～200
掲載論文のDOI（デジタルオブジェクト識別子） 10.1017/S1431927620024824	査読の有無 無
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 －

1．著者名 Younis Mahmoud A.、Khalil Ikramy A.、Elewa Yaser H.A.、Kon Yasuhiro、Harashima Hideyoshi	4．巻 331
2．論文標題 Ultra-small lipid nanoparticles encapsulating sorafenib and midkine-siRNA selectively-eradicate sorafenib-resistant hepatocellular carcinoma in vivo	5．発行年 2021年
3．雑誌名 Journal of Controlled Release	6．最初と最後の頁 335～349
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.jconrel.2021.01.021	査読の有無 無
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1．著者名 Kimura Seigo、Khalil Ikramy A.、Elewa Yaser H.A.、Harashima Hideyoshi	4．巻 330
2．論文標題 Novel lipid combination for delivery of plasmid DNA to immune cells in the spleen	5．発行年 2021年
3．雑誌名 Journal of Controlled Release	6．最初と最後の頁 753～764
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1．著者名 Masum Md. Abdul、Ichii Osamu、Elewa Yaser Hosny Ali、Otani Yuki、Namba Takashi、Kon Yasuhiro	4．巻 11
2．論文標題 Vasculature-Associated Lymphoid Tissue: A Unique Tertiary Lymphoid Tissue Correlates With Renal Lesions in Lupus Nephritis Mouse Model	5．発行年 2020年
3．雑誌名 Frontiers in Immunology	6．最初と最後の頁 1-10
掲載論文のDOI（デジタルオブジェクト識別子） 10.3389/fimmu.2020.595672	査読の有無 無
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2．論文標題 Unique Running Pattern and Mucosal Morphology Found in the Colon of Cotton Rats	5．発行年 2020年
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２．発表標題
Functional attribution of mediastinal fat-associated lymphoid clusters’ innate immune cells in papain induced lung asthma mouse model

３．学会等名
The 1st academia on Japanese veterinary anatomists.

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〔図書〕　計0件

〔産業財産権〕

〔その他〕

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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