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

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研究課題名（和文）Elucidating the role of extracellular vesicles microRNA cargo in HIV associated immune dysfunction

研究課題名（英文）Elucidating the role of extracellular vesicles microRNA cargo in HIV associated immune dysfunction

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　3,500,000円

研究成果の概要（和文）：HIV感染者の細胞外小胞に免疫調節miRNAの特定パターンを発見しました。これによりHIV病因と慢性炎症の理解が進む可能性があります。invitroモデルでEV由来miRNAがサイトカイン分泌に影響することを示し、いくつかのmiRNAが血漿炎症マーカーと関連していることも確認しました。これらのmiRNAは非侵襲的バイオマーカーとして有望です。

研究成果の学術的意義や社会的意義
Identifying distinct miRNA patterns in EVs from HIV-infected individuals enhances our understanding of mechanisms for HIV pathogenesis. These findings can enhance treatment strategies and improve the quality of life for HIV-infected individuals by managing HIV-related inflammation.

研究成果の概要（英文）：We have identified distinct patterns of immunoregulatory miRNA in extracellular vesicles from HIV-infected individuals which may aid to advance our knowledge on HIV pathogenesis and the related chronic inflammation. We successfully developed an invitro model that demonstrated the effects of EV derived miRNAs in cytokine secretion from THP-1 derived microphages. Additionally, we showed that some of the immunoregulatory microRNA levels in EVs were significantly associated with plasma inflammatory markers. These miRNAs could serve as non-invasive biomarkers for HIV status and progression, opening potential for targeting specific miRNAs to control inflammation in HIV patients. The next steps include studying other cell lines to confirm miRNA impact across different environments, validating miRNA roles in cytokine secretion with functional studies and clinical samples, investigating how miRNAs modulate cytokine expression for deeper insights and therapy.

研究分野：Infection and Immunity

キーワード：MiRNA　HIV related inflammation

様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９（共通）

１．研究開始当初の背景

MicroRNAs (miRNAs) are highly conserved small, single-stranded, noncoding RNA molecules that control gene expression by targeting mRNAs for degradation or translational repression. They can be secreted into extracellular fluids within lipid membrane-enclosed vesicles or complexed with proteins, serving as a means of cell-to-cell communication. Dysregulated circulating miRNAs have been associated with various pathological conditions, including cancers, cardiovascular diseases, and neurological diseases. In HIV infection, despite only a small fraction of CD4+ cells being infected, abnormalities and pathological changes are observed in uninfected immune cells and other tissues, leading to immune system dysfunction, chronic inflammation, and organ pathologies. Intercellular and inter-tissue communication mediated by miRNAs delivered by extracellular vesicles may contribute to the systemic nature of HIV disease.

２．研究の目的

The aim of this study was to comprehensively analyze the role of dysregulated extracellular vesicle-delivered miRNAs in immune dysfunction and chronic inflammation during HIV infection. Specifically, we sought to identify distinct miRNA patterns in extracellular vesicles from HIV-infected individuals, investigate their effects on cytokine secretion, and explore their potential as non-invasive biomarkers for HIV status and progression.

３．研究の方法

Plasma samples were obtained from a cohort of adult HIV-infected and uninfected individuals in Tanzania. Only patients without symptoms of acute bacterial, parasite, or viral infections during sample collection were included in this project.

４．研究成果

<u>miRNA Analysis and Associations with plasma inflammatory markers</u>

Using RT PCR targeting over 20 immunoregulatory miRNA Extracted from EVs, we identified distinct patterns of immunoregulatory miRNAs in EVs from HIV-infected individuals. We demonstrated significant associations between the levels of certain miRNAs in EVs and plasma inflammatory markers. These findings suggest that specific miRNAs could serve as non-invasive biomarkers for HIV status and progression.

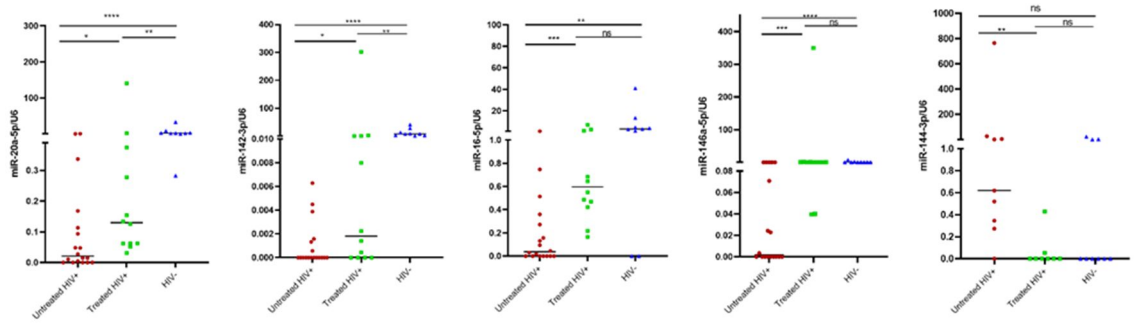

Figure 1 Relative expression of Immunoregulatory miRNAs from plasma EV. Of the selected 20mi RNAs, differential expression levels of miR-20a-5p, miR-142-3p, miR-144-3p, miR-146a-5p and miR-16-5p were observed between HIV Infected and uninfected group.

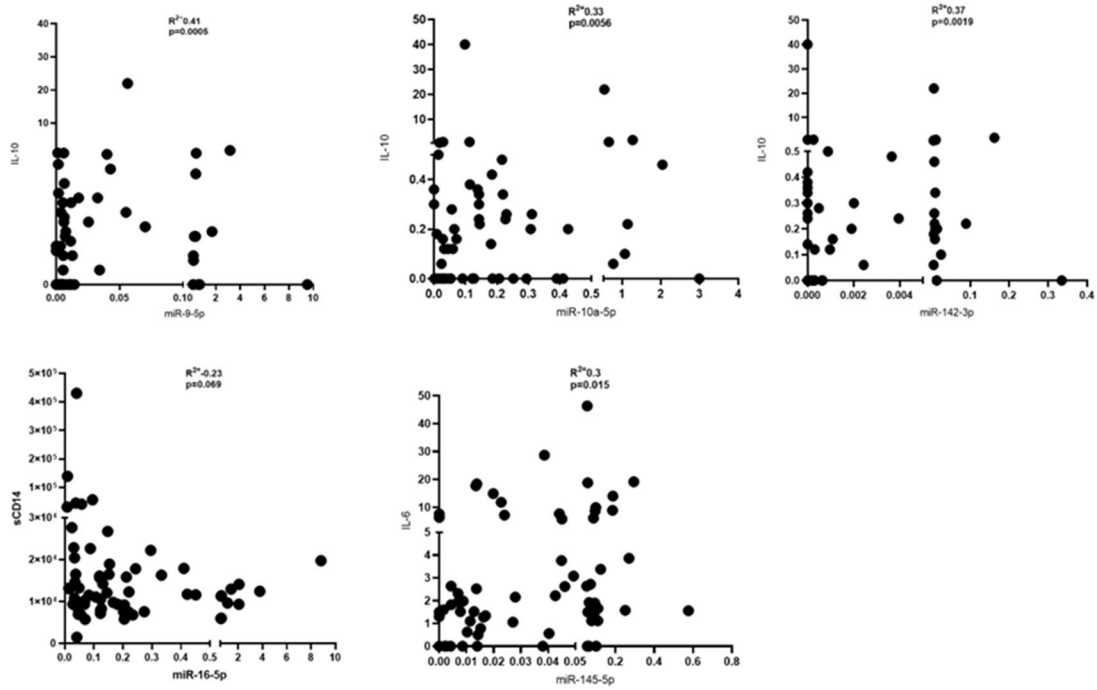

Figure 2; Correlation of inflammatory biomarkers and EV miRNA levels. A number of EV miRNA showed a moderate, but statistically significant association with plasma cytokine levels in virally suppressed patients.

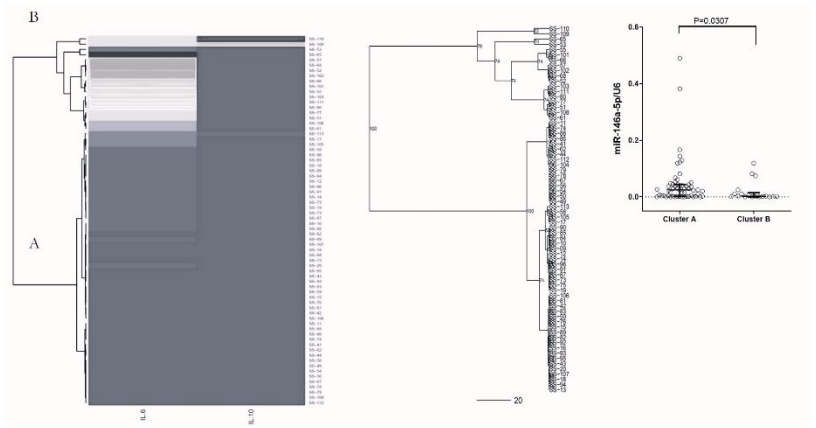

Figure 3; Distinct cluster of patients based on plasma cytokine levels (IL6 and IL10) in virally suppressed patients showed that miR-146a-5p was highly expressed in low cytokine cluster (cluster a) compared to high cytokine cluster (cluster B).

Cytokine Expression Studies

We assessed cytokine production in response to EVs from HIV-infected patients. We successfully developed an in vitro model to investigate the effects of extracellular vesicle (EV)-derived miRNAs on cytokine secretion from THP-1 derived macrophages. This model allowed us to simulate and analyze the interactions between EV-derived miRNAs and immune cells, providing insights into their role in HIV pathogenesis and related chronic inflammation.

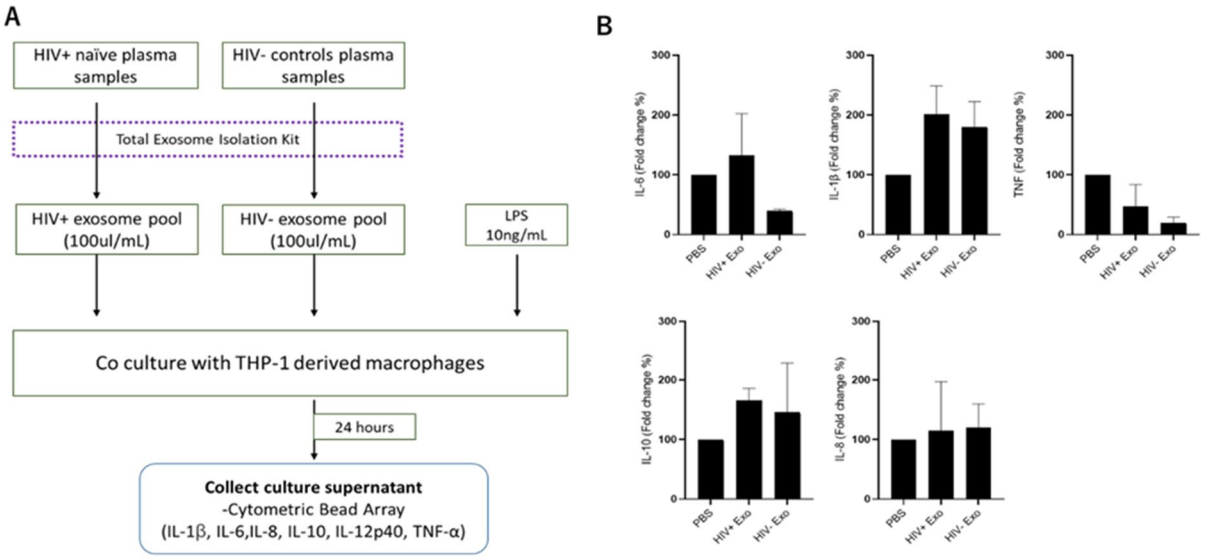

Figure 4. Impact on EVs on expression of cytokines in THP-1 delivered microphage. A) Invitro approach for cytokine expression analysis b) Effect of pooled extracellular vesicles from HIV + and HIV – patients on cytokine secretion in THP-1 macrophages

５．主な発表論文等

〔雑誌論文〕　計0件

〔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 Mussa Bago, Godfrey Barabona, Doreen Kamori, Lilian Nkinda,Takamasa Ueno1.
２．発表標題 The role of dysregulated extracellular vesicles’ miRNAs in the modulation of chronic Inflammation during HIV infection.
３．学会等名 Kumamoto AIDS seminar
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1件

国際研究集会	開催年
MUHAS scientific conference	2023年～2023年

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			
タンザニア	MUHAS			