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СНИЖЕНИЕ НАИВНЫХ MAIT-КЛЕТОК И НЕПОЛНАЯ ИММУННАЯ РЕКОНСТИТУЦИЯ У ПАЦИЕНТОВ С ВИЧ-1, ПОЛУЧАЮЩИХ ТЕРАПИЮ

Резюме
В работе исследованы иммунологические механизмы, лежащие в основе неполной иммунной реконституции у пациентов с ВИЧ-1, получающих антиретровирусную терапию. С использованием одноклеточного РНК-секвенирования и анализа репертуара Т-клеточных рецепторов периферических мононуклеарных клеток крови были выявлены различные иммунные профили у иммунологических нереспондеров, иммунологических респондеров и здоровых доноров. Исследование показало значительное снижение наивных мукозо-ассоциированных инвариантных Т-клеток (MAIT) у нереспондеров; этот результат был подтверждён в модели симийного иммунодефицитного вируса у макак-резусов. Транскриптомный анализ выявил нарушение цитотоксической функции и усиление сигнального пути TGF-β в MAIT-клетках у нереспондеров, что указывает на наивные MAIT-клетки как на потенциальную терапевтическую мишень для улучшения иммунной реконституции.

Ключевые слова: вирус иммунодефицита человека (ВИЧ), иммунная реконституция, иммунологический ответ, репертуар Т-клеточных рецепторов, одноклеточное РНК-секвенирование.

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REDUCED NAÏVE MAIT CELLS AND INCOMPLETE IMMUNE RECONSTITUTION IN TREATED HIV-1 PATIENTS

Resume

Investigated the immunological mechanisms underlying incomplete immune reconstitution in antiretroviral therapy–treated HIV-1 patients. Using single-cell RNA sequencing and T-cell receptor repertoire analysis of peripheral blood mononuclear cells, distinct immune profiles were identified between immunological non-responders, immunological responders, and healthy controls.

The study revealed a significant reduction in naïve mucosal-associated invariant T (MAIT) cells in non-responders, a finding validated in a simian immunodeficiency virus rhesus macaque model. Transcriptomic analysis demonstrated impaired cytotoxic function and enhanced TGF-β signaling in MAIT cells from non-responders, highlighting naïve MAIT cells as a potential target for improving immune reconstitution.

Keywords: Human immunodeficiency virus (HIV)**,** immune reconstitution**,** immunological response**,** T-cell receptor repertoire**,** single-cell RNA sequencing

Abstract

Incomplete immune reconstitution affects 10%–40% of HIV patients receiving antiretroviral therapy (ART), yet the underlying immunological features of these immunological non-responders (INRs) remain poorly defined. Using single-cell RNA sequencing and paired T-cell receptor profiling of peripheral blood mononuclear cells, we compared immune landscapes among INRs, immunological responders (IRs), and healthy controls. INRs exhibited a marked reduction in mucosal-associated invariant T (MAIT) cells, particularly the naïve MAIT subset, a finding validated in simian immunodeficiency virus–infected rhesus macaques. MAIT cells in INRs were predominantly $CD8^+$ and displayed reduced expression of cytotoxic genes alongside enhanced TGF-β signaling–related pathways. These results associate naïve MAIT cell deficiency with impaired immune recovery in ART-treated HIV patients, identifying a potential cellular target for improving immune reconstitution.

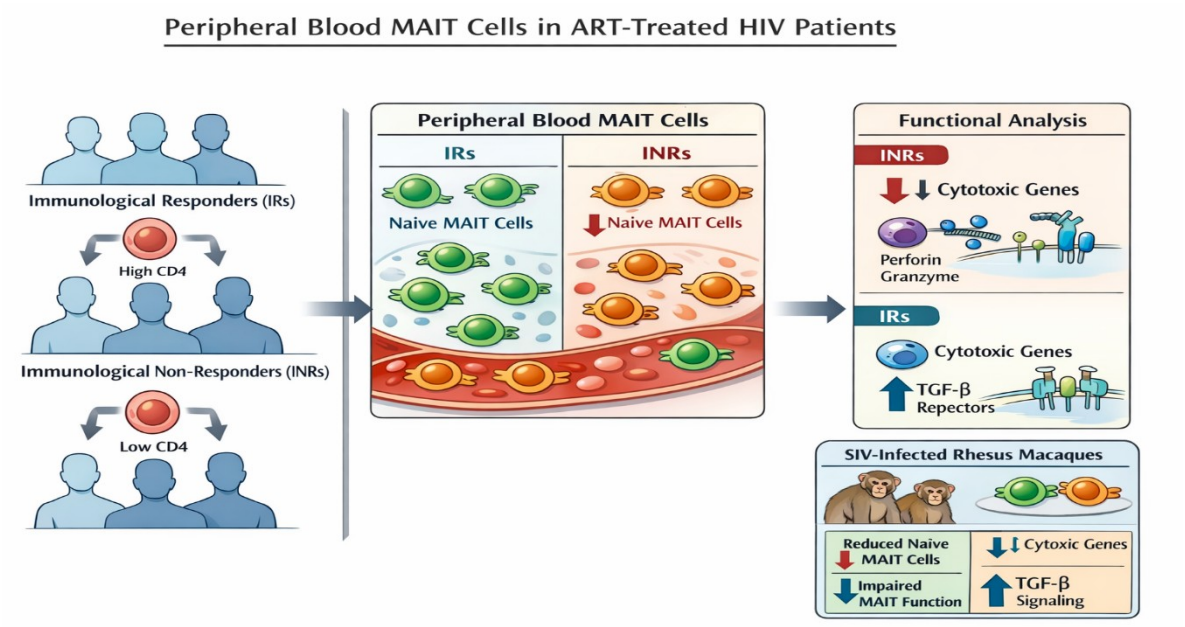
Introduction

Sustained antiretroviral therapy (ART) is the cornerstone of human immunodeficiency virus (HIV) management and can effectively suppress viral replication while restoring $CD4^+$ T-cell counts to levels comparable to those observed in healthy individuals (Yang et al., 2021; Menendez-Arias and Delgado, 2022; Mao et al., 2024). However, considerable heterogeneity exists in immunological outcomes among ART-treated patients. While some individuals achieve robust $CD4^+$ T-cell recovery alongside virological suppression and are classified as immunological responders (IRs), others fail to reconstitute $CD4^+$ T-cell counts despite effective viral control; these patients are referred to as immunological non-responders (INRs) (Zhang et al., 2024; Mou et al., 2025).

Persistent $CD4^+$ T-cell depletion in INRs is frequently accompanied by compromised immune function, predisposing these individuals to opportunistic infections and increasing the risk of progression to acquired immune deficiency syndrome (AIDS) (Liu et al., 2025). The mechanisms underlying incomplete immune reconstitution are multifactorial and remain incompletely understood.

Contributing factors include impaired bone marrow hematopoiesis, reduced thymic output, residual viral replication, chronic immune activation, and dysregulated cytokine production (Yang et al., 2020).

Previous studies have demonstrated a positive correlation between peripheral $CD4^+$ T-cell counts and the proliferative capacity of bone marrow hematopoietic progenitor cells (HPCs) and hematopoietic stem cells (HSCs). Notably, INRs exhibit significantly reduced colony-forming potential of HPCs and HSCs compared with IRs, indicating defective hematopoietic function in these individuals (Guo et al., 2016). In addition, diminished thymic output results in a reduced pool of naïve $CD4^+$ T cells, which has been implicated as a key contributor to impaired immune reconstitution during HIV infection (Carvalho-Silva et al., 2020). Moreover, inhibitory receptor–driven $CD4^+$ T-cell exhaustion has been linked to suboptimal immune recovery in ART-treated patients (Noyan et al., 2018; Vos et al., 2024). Beyond adaptive immunity, persistent activation of innate immune cells—including natural killer cells, monocytes, and macrophages—may further influence immune reconstitution during ART (Mensching and Hoelzemer, 2022).Figure-1.



Despite extensive research, the precise mechanisms governing immune pathway modulation and the balance of T-cell subsets during discordant immunological responses to ART remain incompletely understood (Yang et al., 2020). Mucosal-associated invariant T (MAIT) cells represent an evolutionarily conserved population of unconventional T lymphocytes characterized by the expression of a semi-invariant αβ T-cell receptor (TCR). These cells function at the interface of innate and adaptive immunity and rapidly secrete diverse cytokines and cytotoxic effector molecules following activation through both TCR-dependent and TCR-independent pathways (Su et al., 2022).

Multiple studies have demonstrated a marked decline in MAIT cell frequency during both acute and chronic HIV infection. Although MAIT cells are not preferentially targeted by HIV, their depletion is thought to result from tissue redistribution, sustained activation, functional exhaustion, and subsequent long-term attrition (Han et al., 2022; Xia et al., 2022). During early HIV-1 infection, MAIT cells undergo transient activation and expansion in peripheral blood and mucosal tissues concurrent with peak viremia, likely driven by increased microbial translocation. This phase is followed by partial viral control as viremia stabilizes at a setpoint, and subsequently by a progressive loss of MAIT cell function during chronic infection (Lal et al., 2020).

Materials and Methods

Peripheral blood samples were obtained from ART-treated HIV-1–infected individuals classified as immunological non-responders (INRs) or immunological responders (IRs) based on $CD4^+$ T-cell recovery, as well as from age- and sex-matched healthy controls (HCs). All HIV-1–infected participants maintained sustained viral suppression under ART. Peripheral blood mononuclear cells (PBMCs) were isolated using density-gradient centrifugation.PBMCs were processed for single-cell RNA sequencing (scRNA-seq) and paired single-cell T-cell receptor (TCR) repertoire sequencing using a droplet-based platform following the manufacturer's protocols. Libraries were sequenced on a high-throughput sequencing system. Raw sequencing data were processed using standard pipelines for quality control, normalization, dimensionality reduction, and cell clustering. TCR clonotypes were assigned and analyzed in parallel with transcriptomic data.

Discussion

In this study, we characterized immune cell heterogeneity associated with incomplete immune reconstitution in ART-treated HIV-1 patients using single-cell multi-omics approaches. Our data reveal a pronounced reduction in MAIT cells in INRs, with a particularly marked loss of the naïve MAIT cell subset. This alteration was consistently observed in both human cohorts and an SIV-infected rhesus macaque model, suggesting a conserved immunological phenomenon.

MAIT cells are critical mediators at the interface of innate and adaptive immunity and play an important role in antimicrobial defense and immune regulation. Although MAIT cells are not directly infected by HIV, chronic immune activation, microbial translocation, and sustained antigenic stimulation during HIV infection are thought to drive their activation, exhaustion, and eventual depletion. Our findings extend previous observations by demonstrating that impaired immune reconstitution is specifically associated with a deficiency in naïve MAIT cells, rather than a uniform loss of all MAIT subsets.

Together, these results support a model in which disrupted MAIT cell homeostasis —particularly at the naïve stage—contributes to impaired immune reconstitution in a subset of ART-treated patients. Targeting pathways that preserve or restore MAIT cell function may therefore represent a novel therapeutic strategy for improving immune recovery in INRs.

Conclusion: This study provides a comprehensive single-cell characterization of immune dysregulation in ART-treated HIV-1 patients with incomplete immune reconstitution. We identify a significant reduction in naïve MAIT cells as a distinguishing feature of immunological non-responders and demonstrate associated functional alterations at the transcriptional level. These findings highlight naïve MAIT cells as a potential cellular determinant of immune recovery and suggest new avenues for therapeutic intervention aimed at enhancing immune reconstitution in HIV-1–infected individuals.

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