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Cofilin, an intracellular marker for HIV-associated CD4 T cell motility dysregulation, shed light on the mechanisms of incomplete immune reconstitution in HIV patients

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Advances in antiretroviral therapy (ART) have turned HIV infection from a death sentence into a manageable chronic disease. Finding a cure for HIV has become an urgent global priority as there are approximately 37 million people worldwide living with HIV infection. Immunotherapies holds the potential to achieve a long-lasting effect on viral control, i.e. a functional cure. However, such therapies require significant reconstitution of immune cells, which cannot be accomplished by ART alone. Because Gut-associated lymphoid tissue (GALT) harbors the majority of CD4 T cells in the body, HIV infection causes a rapid depletion of CD4 T cells from the GALT[1]. Despite full suppression of plasma viremia and evidence of immune reconstitution in the peripheral blood, most HIV patients on ART continue to have severe depletion of CD4 cells in their lymphoid tissues[2]. The mechanisms underlying this disparity of CD4 T cell repopulation in peripheral blood versus lymphoid tissues in HIV patients on ART are largely unknown. Additionally, it is unclear why the circulating CD4 T cells fail to replenish their tissue counterparts in HIV patients. These abnormalities are likely related to the impact of HIV infection on CD4 T cell trafficking in and out of lymphoid tissues and the tissue's instructions for migration and retention of CD4 T cells.

In the recent issue of Science Advances[3], He and co-authors conducted a study to investigate cofilin phosphorylation and the motility of peripheral blood CD4 T cells in a large cohort of HIV patients (n=193) versus healthy controls (n=100). Cofilin is an actin depolymerizing factor that depolymerizes filamentous actin (F-actin) and is inactivated by phosphorylation. Cofilin is a major cell motility engine that drives T cell motility for cell circulation and homing to lymphoid and non-lymphoid tissues[4]. In the He study, the authors found that cofilin phosphorylation was markedly reduced, thereby becoming hyperactivated, in the peripheral blood resting CD4 T cells of HIV patients versus heathy controls. Additionally, cofilin hyperactivation persisted in HIV patients on ART and was associated with poor CD4 T cell recovery in these patients. These results indicate that, irrespective of ART, T cell motility is impaired in HIV patients. The authors speculated that cofilin hyperactivation was mainly attributed to two factors including (1) early signaling from HIV gp120 binding to the chemokine coreceptor CXCR4 or CCR5 during the acute phase of infection[5], and (2) persistent signaling from chronic immune activation in the disease course[6]. The authors

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further speculated that the defective set point of CD4 T cell motility might be established early in HIV infection, which might be exacerbated by immune activation and inflammation during chronic HIV infection.

Two earlier pilot studies with smaller sample sizes suggested that cofilin hyperactivation occurred in the blood resting CD4 T cells of HIV patients[6,7]. These studies demonstrated that the resting CD4 T cells from HIV patients carried significantly higher levels of active cofilin and that the hyperactivated cofilin was likely associated with immune activation in HIV patients[6,7]. Consistent with these studies, the He et al. study used a large cohort to more conclusively demonstrate a direct linkage between cofilin hyperactivation and the impairment of CD4 T cell migration. The authors used R10015, a cofilin kinase inhibitor, to quantify direct effects of cofilin hyperactivation on T cell motility and found that a 50% reduction in cofilin phosphorylation could cause a 20%−40% decrease in T cell migration. They also used anti-human α4β7 integrin antibody to modulate the cofilin activity and found that the motility of blood resting CD4 T cells from HIV patients was partially restored. Thus, He *et al*. suggested that cofilin would represent a potential target for therapeutic intervention to restore T cell motility for T cell tissue repopulation and immune reconstitution in HIV patients.

CD4 T cells are heterogeneous population consisting of several subsets such as follicular helper T (Tfh), Th1, Th2, Th9, Th17, and regulatory T cells. The He study solely focused on resting blood CD4 T cells that would contain all CD4 subpopulations. Because the majority of HIV infection occurs in lymphoid tissue, it will be interesting to study the role of T cell motility in specific tissue CD4 subpopulations and their relationship to HIV. One such lymphoid CD4 subset, the Tfh subset, has been identified as a major CD4 compartment for HIV infection and replication[8,9]. Strikingly, infected Tfh cells expand rather than decline and subsequently become a major virus reservoir in HIV patients[8,9]. We conducted whole transcriptome RNA sequencing of Tfh cells ($CD3^+CD4^+CXCR5^+PD\text{-}1^{high}$) and non-Tfh cells ($CD3^+CD4^+CXCR5^-PD\text{-}1^-$) from human tonsil tissues and found that the expression of cell motility-related genes was different between these two subpopulations. As shown in the Figure, 4 genes (TNS4, DOCK6, COL1A2, and LAMA5) had >2-fold higher expression and 7 genes (COL1A1, CFL2, LAMA3, ERBB3, LAMA3, COL5A1, and EREG) had <2-fold lower expression in Tfh cells than non-Tfh cells. Thus, studies are warranted to investigate whether there is a link between Tfh cell motility-related genes, such as Cofilin, and the mechanisms underlying HIV reservoir in infected Tfh cells. Moreover, this data emphasizes the need to examine T cell motility in subsets within the resting CD4 population rather than in the CD4 population as a whole.

The He et al study has opened a new avenue for monitoring CD4 T cell motility in HIV patients. Their results provide insights for the development of novel therapeutics to restore T cell migration and tissue repopulation for immune reconstitution and immune control of viremia in HIV patients. Nevertheless, there are still several key questions that need to be addressed. Future studies are warranted to investigate the cellular factors and signaling pathway responsible for cofilin hyperactivation. In addition, the impact of cofilin dysfunction on the homeostasis of individual CD4 T cell subsets, such as Tfh cells, in HIV patients needs to be studied.

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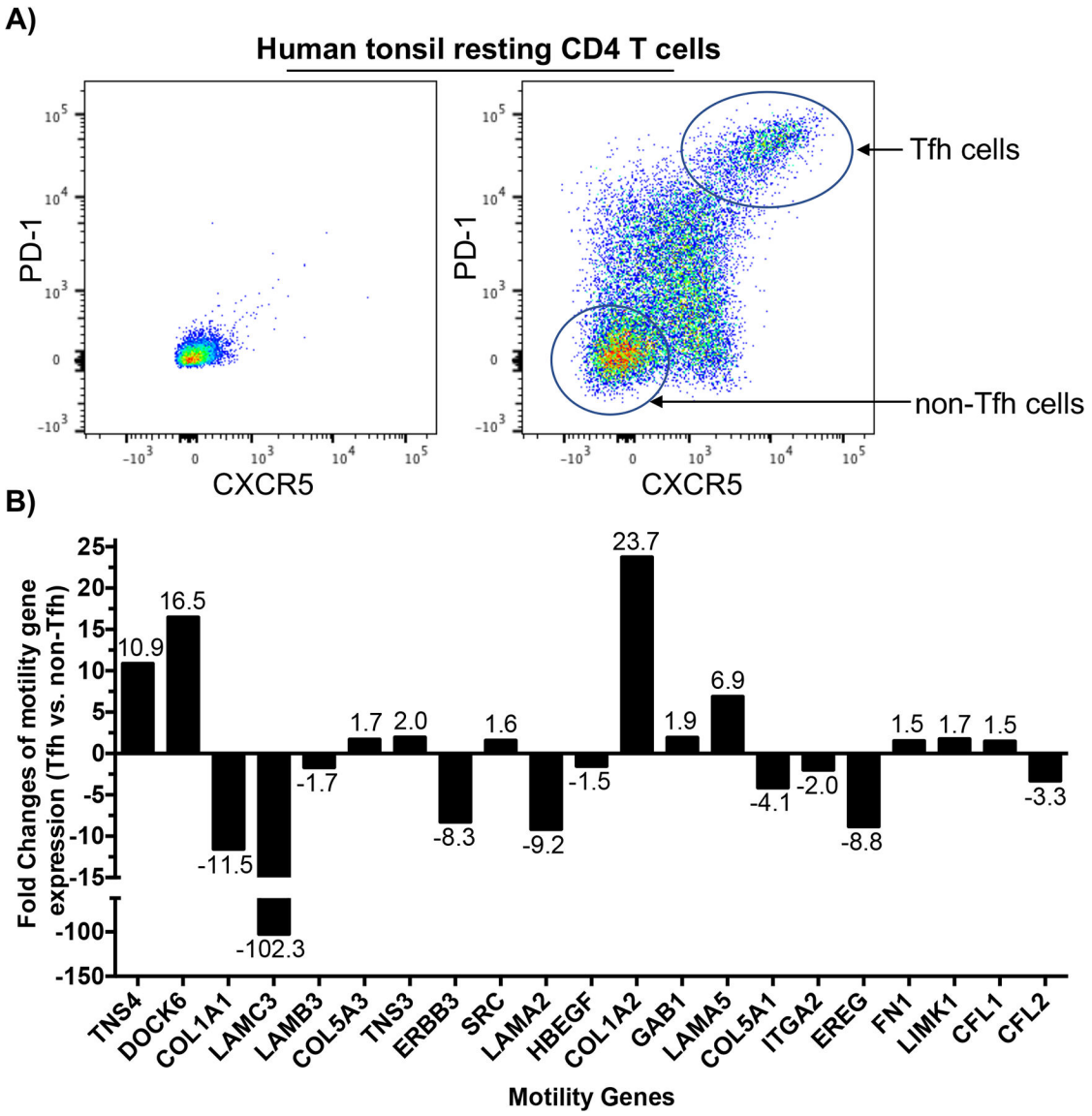

Figure.

Expression of cell motility-related genes in Tfh versus non-Tfh subsets. Mononuclear cells were isolated from human tonsils from patients experiencing tonsil stone, and subsequently subjected to isolation of CD4 T cells using the Pan T Cell Isolation Kit II (Miltenyi Biotec, Auburn, CA) as previously described 10, which yielded >95% purity of T cells as assessed by flow cytometric analysis for the proportion of CD3 T cells. (A) Isolated CD4 T cells were incubated with fluorochrome-conjugated antibodies against human CD3, CD4, CXCR5, and PD-1 (right plot) or isotype controls (left plot). Tfh cells (CD3+CD4+CXCR5+PD−1high) and non-Tfh cells (CD3+CD4+CXCR5−PD−1−) were separately sorted out for RNA extraction. (B) The RNA extractions were used for whole transcriptome RNA sequencing. Analysis of cell motility-related genes was carried out using the Reactome software. The number on the top of each bar graph indicates the folddifference between Tfh cells versus non-Tfh cells. The data was obtained from 3 tonsil tissue donors (n=3).