The Intimate Relationship Between CD4⁺ T Cell Morphology and HIV-1 Infection

Robert L. Furler and Douglas F. Nixon

FIG. 1. Migrating Human CD4⁺ T cells have a polarized morphology. Primary human CD4⁺ T cells coated on a fibronectin-coated coverslip were cocultured with (A) macrophages and (B) dendritic cells and imaged by Scanning Electron Microscopy. When in contact with extracellular matrix components like fibronectin, CD4⁺ T cells polarize their morphology to optimize signaling cascades and mechanical function. The T cells in these micrographs are elongated with three visible sections: the leading edge, the nucleus, and the uropod. These cellular compartments play critical roles in HIV-1 entry, replication, and budding.

Keywords: HIV-1, uropod, leading edge, T cell morphology

HUMAN CD4⁺ T CELLS MIGRATE through the lymphatics and inflamed tissue by polarizing their morphology as seen in these scanning electron micrographs of CD4⁺ T cells (Fig. 1), which can be seen with (A) a macrophage or (B) a dendritic cell process on fibronectin-coated coverslips as previously described.¹ The CD4⁺ T cell morphology can be visibly divided into three components: the leading edge, the nucleus, and the uropod. This cell shape allows for compartmentalization of signaling cascades and polarization of membrane receptors, which are important for coordinating the protrusive and contractile motions required for leukocyte chemotaxis. At the leading edge, G protein-coupled receptors (GPCRs) and adhesion receptors are activated by chemokines, the extracellular matrix, and other environmental mediators to provide migratory directionality. These signals are transmit-

ted to downstream signaling GTPases Rac1 and CDC42, which induce actin-rich lamellipodia and filopodia at the leading edge, respectively, while simultaneously activating RhoA in the rear of the cell. The lamellipodia, seen as the ruffled edge in the micrographs, contain chemokine receptors such as CCR5 and CXCR4, members of the GPCR superfamily and coreceptors for HIV-1 entry.

Immediately posterior to the lamellipodia is the globular nucleus. The nucleus is tethered to the leading edge through the cytoskeleton and is pulled forward as the cell migrates. After viral entry and reverse transcription of the HIV-1 genome, the pre-integration complex enters the nucleus. The integrated provirus is then transcribed into multiply-spliced mRNAs which are then translated into the Tat, Nef, and Rev proteins. These early expressed proteins have been

shown to alter both cytoskeletal and signaling complexes that are typically compartmentalized in the migrating CD4⁺ T cell. HIV-1 Tat and Nef both alter the actin cytoskeleton and the Rac1/CDC42/RhoA axis; however, interpretation of published findings needs to take into account cell type used and whether the viral protein is produced intracellularly or added exogenously. These early proteins may alter the cytoskeleton to optimally produce viral structural proteins and virions.

Behind the nucleus is the tail-like structure termed the uropod, which contains the centrosome and the majority of membrane-bound organelles including the endoplasmic reticulum and Golgi apparatus, which are where structural proteins such as HIV-1 Env are produced and processed. In addition, several host proteins and lipids that are incorporated into the HIV-1 virion are localized to the uropod, including ICAM-1, CD44, CD43, MHC-I, CD55, CD59, Ezrin, Moesin, Flotillin, and Cofilin.² Viral proteins including Gag and viral RNA have also been shown to localize at the uropod, where PI_{(4,5)P}₂ cholesterol-rich lipid rafts reside,³ which provides further evidence for virion production at the uropod. Marooka *et al.* reported extended uropod structures in HIV-1-infected cells,⁴ which could arise from an actin–myosin contraction defect elicited by HIV Nef, Gag, and Vpu-dependent modulation of RhoA/ROCK activity.

With the wealth of literature on how HIV-1 proteins interact with the cytoskeleton and impacts signaling cascades, it is important to understand the four-dimensional structure of the CD4⁺ T cell as it leaves the blood stream and migrates through the lymphatics and inflamed tissue. Compartmentalization of the cytoskeleton, organelles, and signaling cascades is likely not only required for T cell function but also for virion production.

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Address correspondence to:

Robert L. Furler, PhD

Division of Infectious Diseases

Department of Medicine

Weill Cornell Medicine

413 East 69th Street, Belfer Research Building 528

New York, NY 10021

E-mail: rlf2001@med.cornell.edu