CHAPTER 1

FOXO1, T-Cell Trafficking and Immune Responses
Florent Carrette, Stéphanie Fabre and Georges Bismuth*

Abstract

Efficient T-cell adaptive immune response require a faultless coordination between migration of naive T-cells into secondary lymphoid organs and critical biological outcomes driven by antigen such as cell division and cell differentiation into effector and memory cells. Recent works have shown that the phosphoinositide 3-kinase (PI3K) pathway could govern several of these processes. In this control, transcriptional factors of the Forkhead box O (FoxO) family, in particular FOXO1, a downstream effector of PI3K, appears to play a major role by coordinating both cellular proliferation of T-cells after antigen recognition and expression of homing molecules essential for their trafficking in the body.

Introduction

Efficient immune surveillance requires that naive T-lymphocytes circulate permanently between the blood stream, secondary lymphoid organs and lymphatic vessels. It has been estimated that at a given time the pool of T-cells in the blood represents only 5% of the total T-cell count, 70% of them being localized in lymph nodes and approximately 20% in the spleen. In normal conditions, a T-cell usually stays less than 30 minutes in the blood circulation, making repeated visits of several hours in secondary lymphoid organs. Because of the limited number of specific T-lymphocytes for a given antigen, this trafficking is fundamental to increase the probability for a T-cell to encounter the antigen and thereby warrant immunological surveillance of the body. Moreover, antigen-presenting cells (APC), especially dendritic cells (DCs) (the only APC that can activate naive T-cells), migrate preferentially into lymph nodes after the capture of foreign antigens in tissues at the periphery. Thus, lymph nodes occupy a strategic position at the crossroads of the blood and lymphatic vessels to bring together in an adapted microenvironment these different actors of the immune response. This trafficking of T-cells, the so called homing process, is tightly controlled by a set of coordinated mechanisms, notably involving cell surface molecules and soluble signals such as chemokines. We will describe in this chapter the mechanisms by which this spatiotemporal control can be exercised at the different steps of a T-cell response and consider very recent discoveries showing that the Foxhead box O transcriptional factor FOXO1, one major downstream effectors of the PI3K pathway, has an unanticipated role in these regulations.

Mechanisms of T-Cell Homing into Lymph Nodes

T-lymphocytes migrate into lymph nodes by crossing the vascular endothelium at the level of specialized postcapillary vessels, termed high endothelial venules (HEV). This passage is based on a hierarchical sequence of interactions between lymphocytes and endothelial cells,

*Corresponding Author: Georges Bismuth—Institut Cochin. 22 rue Méchain, 75014, Paris, France. Email: bismuth@cochin.inserm.fr

Figure 1. The different steps of T-cell transmigration. In HEV L-selectin expressed at tips of T-cell microvilli can interact with peripheral node addressins (PNAd) like CD34 or GlyCAM-1 decorated with carbohydrates. A rolling movement along the endothelium that slows down the cell and allows firm adhesion follows this initial anchoring. The integrin LFA-1 (Leukocyte Function-associated Antigen-1) and the adhesion molecule ICAM-1 (Intercellular Adhesion Molecule-1) expressed on T-cells and endothelial cells, respectively, are the two key receptors involved during this phase. However, in resting T-cells, the avidity of LFA-1 for its ligand is weak and the T-cell needs supplementary signals to transmigrate at the level of the HEV. These signals are triggered by chemokines present on endothelial cells (such as CCL19 or CCL21) that interact with CCR7 on T-cells and strongly increase the avidity of LFA-1 for ICAM-1.

governed by adhesion molecules, such as selectins and integrins and signals given by chemokines (Fig. 1). L-selectin, a Type C lectin of ~90 kDa also named CD62-L or LAM-1 (Leukocyte Activated Molecule-1), is a key player in this process. It was discovered nearly two decades ago as a glycoprotein involved in the interaction of leukocytes with the endothelium of lymph nodes and inflamed tissues.\(^1\) L-selectin is expressed at the end of plasma membrane microvilli and specifically interacts with sialylated oligosaccharides carried by molecules like CD34 and glycosylation-dependant cell adhesion molecule-1 (GlyCAM-1) (also called PNAd for peripheral node addressins), constitutively expressed on the surface of HEV endothelial cells. Invalidation of the L-selectin gene in the mouse has demonstrated the essential role played by this molecule in the migration of leukocytes into secondary lymphoid organs in vivo.\(^4\) Deficient mice show a severe reduction of the number of T-lymphocytes in lymph nodes, as well as a defect of primary immune responses to antigen. Lymphocytes from these mice cannot adhere to the HEV anymore, indicating that the interaction between L-selectin and its vascular ligands is essential for later stages of transendothelial migration.

According to this central role played by L-selectin in the migration of T-cells within lymph nodes, the mechanisms regulating its membrane expression were the subject of many studies. L-selectin expression is rapidly down-modulated (in a few tens of minutes) after T-cell receptor (TCR) triggering by antigen\(^5\) and activated T-cells always express reduced levels of L-selectin.\(^6\) Our knowledge of the molecular mechanisms controlling this rapid decrease, early after activation, is still partial but the use of pharmacological inhibitors has revealed the involvement of metalloproteases from the extracellular matrix,\(^7\) with as a potential, but not exclusive candidate, the ADAM17 metalloprotease (also known as CD156b or TNF-\(\alpha\) converting enzyme).\(^8\) The contribution of L-selectin proteolysis in T-cell homing was unambiguously demonstrated by the study of transgenic mice expressing a shedding-resistant L-selectin molecule.\(^9\) While these mice do not present abnormalities in the cellular composition of secondary lymphoid organs, suggesting that the cleavage of L-selectin is not required for the migration of naive T-lymphocytes into