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Nuclear envelope lamin-A as a coordinator of T cell activation

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Abbreviations: APC, antigen-presenting cell; CHS, hapten-induced contact hypersensitivity; cSMAC, central supramolecular activation cluster; DCs, dendritic cells; ERK1/2, extracellular signal-related kinase 1/2; GEF, guanine nucleotide exchange factor; IL-2R, IL-2 receptor; INM, inner nuclear membrane; IS, immunological synapse; iPS, induced pluripotent stem; LAT, linker of activated T cells; LINC, linker of nucleoskeleton and cytoskeleton; MIIA, Myosin IIA; MTOC, microtubule-organizing centre; ONM, outer nuclear membrane; PLCγ1, phospholipase C γ1; pSMAC, peripheral supramolecular activation cluster; SLP-76, SH2 domain-containing leukocyte protein of 76 kD; TCR, T-cell receptor; TIRF, Total internal reflection fluorescence; ZAP-70, ζ-Chain-associated protein of 70 kD

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Nuclear lamins A/C control several critical cellular functions, e.g., chromatin organization, gene transcription, DNA replication, DNA damage responses, cell cycle progression, cell differentiation, and cell polarization during migration. However, few studies have addressed the role of lamins A/C in the control of the functions of immune cells. Recently, we have demonstrated that lamins A/C are induced in T cells upon antigen recognition. Lamins A/C enhance T cell responses by coupling the plasma membrane to the nucleus via the linker of nucleoskeleton and cytoskeleton (LINC) complex and the actin cytoskeleton. Here, we discuss the possible physiological relevance and functional context of lamin A/C in T cell activation and propose a model in which lamins A/C are key modulators of immune cell functions.

A-Type Lamins

The mammalian nuclear envelope separates the nucleoplasm from the cytoplasm. It is composed by the outer and inner nuclear membranes, the nuclear pore complexes and the nuclear lamina.[1] The outer nuclear membrane (ONM) forms a continuum with the endoplasmic reticulum, whereas the inner nuclear membrane (INM) is aligned with the nuclear lamina.[1] Within the nucleus, the nuclear lamina is made of a meshwork of type V intermediate-filament proteins called lamins. It is tightly associated to several INM-associated proteins and interacts with portions of the chromatin.[1] Lamins can be classified as A-type or B-type. They are encoded by different genes: *LMNB1* encodes lamin B1, L*MNB2* encodes lamin B2 and lamin B3 proteins, and *LMNA* encodes the major forms lamin A and C, and also lamins AΔ10 and C2.[1]

A-type lamins provide mechanical stability to the nucleus and have been linked to the regulation of various cellular processes, including nuclear positioning, higher-order chromatin organization, nuclear pore complex organization, gene transcription, nuclear envelope breakdown and reassembly during mitosis, DNA replication, DNA damage response, cell cycle progression, cell differentiation, and cell polarization during migration.[1,2] These functions have been addressed in a variety of cell types, but only a few have been performed in immune cells. In this review, we provide a brief overview of the role of lamins in lymphocytes with emphasis on our recent study demonstrating that lamin A is an important modulator of T cell activation.[3]

Lamin A and T Cell Activation

T cell activation occurs following the recognition of foreign antigens presented by antigen-presenting cells (APCs). During this process, T cells and APCs form cell-cell contacts, called immunological synapses (IS). These specialized cell-cell contacts are characterized by a highly organized structure that enables efficient, transient cell-cell communication.[4,5] IS formation and maintenance involves the controlled recruitment of membrane

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receptors to specific subcellular sites, e.g., an accumulation of the T-cell receptor (TCR) and CD3 at the central supramolecular activation cluster (cSMAC); and an accumulation of actin, integrins, and other adhesion molecules at the surrounding peripheral SMAC (pSMAC). T cell activation also requires translocation of the microtubule-organizing center (MTOC) toward the T cell-APC contact. The repositioned MTOC then directs the polarization of intracellular vesicles to the IS.

Previous studies have reported the absence of lamin A/C in unstimulated human and mouse T lymphocytes.[6,7] Conversely, Rober and collaborators have observed a few lamin A/C-positive lymphocytes from rat bone marrow cultures.[8] Lamin A/C expression has also been reported in activated human peripheral blood lymphocytes, $CD4^+$ T lymphocytes and in $CD30^+$ lymphoid cells.[9-11] We have observed that although few resting human and mouse T lymphoblasts expressed lamin A, its presence was transiently and considerably increased upon T cell activation following cognate immune interactions.[3] The amount of A-type lamins during the interphase of somatic cells is quite stable, exhibiting slow subunit exchange.[12] However, we found a rapid production of lamin A/C mRNA and protein upon T cell activation.[3] This is consistent with the fact that mature lamin A can be formed 2 h after synthesis of the pre-lamin A precursor in other cell types.[1] The specific signaling pathway mediating lamins A/C gene expression remains to be determined. Akt/PKB pathway might play a role in this process, since it is induced during T cell activation,[13] and it is involved in pre-lamin A transcription in interphase of other cell types, possibly through the regulation of the transcription factors FoxO, Sp1/Sp3, AP1 and CREB.[14] In our study, the peak of lamin A/C production in activated T cells was followed by a steep decrease.[3] This decrease could be due to a reduced de novo synthesis and/or an increased degradation of lamin A/C proteins. An additional possibility is that expression in lymphoid cells is controlled by microRNAs. In this regard, lamin A, but not lamin C, levels in the brain are regulated by the microRNA miR-9.[15]

In mice, lamin A/C absence induces severe age-dependent defects in T and B cell development, which have been associated with indirect effects related to the loss of A-type lamins in non-immune cells.[16] However, we observed that splenocytes and $CD4^+$ T cells isolated from spleens of *Lmna*$^{-/-}$ mice exhibited decreased activation in response to different TCR-dependent stimuli[3] (**Fig. 1**), displaying reduced mRNA and protein expression of the T-cell activation markers CD25 (α chain of the IL-2 receptor, IL-2R) and CD69. Also, by using a hapten-induced contact hypersensitivity (CHS) model,[17] we demonstrated that lamin A/C proteins modulate the immune response in vivo. Wild-type irradiated mice reconstituted with bone marrow cells from *Lmna*$^{-/-}$ mice exhibited reduced ear inflammation. Moreover, adoptively transferred wild-type animals displayed reduced accumulation of *Lmna*$^{-/-}$ $CD4^+$ T cells in ears, lymph nodes, and spleens,[3] suggesting that lamin A/C could regulate T cell proliferation and/or migration after antigen recognition.

Ectopic expression of lamin A in the lamin A-deficient human T cell line jurkat increased basal levels of T cell activation upon antigen recognition,[3] enhancing CD25 and CD69 mRNA and protein expression (**Fig. 1**). These results suggest that lamin A modulates T cell activation by triggering changes in protein transcription. In this sense, A-type lamins can modulate gene expression through the interaction with signaling proteins, as ERK1/2 (extracellular signal-related kinase 1/2), and transcription factors, as c-Fos.[1,2] ERK1/2 activation modulates CD69 and CD25 expression,[18] and lamin A expression in jurkat T cells enhances ERK1/2 phosphorylation.[3] Moreover, ERK1/2 inhibition prevents the lamin A-dependent increase in surface CD69 expression (**Fig. 1**), further confirming that lamin A modulates T cell activation by regulating the transcription of T cell activation markers.

Lamin A expression in jurkat T cells also facilitates and stabilizes IS formation, as measured by the quantification of the total number of conjugates and their cell-cell interaction time using confocal and time-lapse confocal microscopy.[3] Using confocal and TIRF (total internal reflection fluorescence) microscopy to analyze the distribution and dynamics of TCR/CD3 complexes at the cSMAC of the IS, we showed that Lamin A ectopic expression in jurkat T cells enhances the dynamic redistribution and internalization of these complexes (**Fig. 1**). It also increases the phosphorylation of CD3 downstream signaling molecules, as PLCγ1 (phospholipase C γ1), Vav1, myosin IIA (MIIA), and ERK1/2 (**Fig. 1**). These data suggest that the lamin A/C-induced increase in intracellular signaling was related to the regulation of the lymphocyte cytoskeleton. Lamin A-expressing cells exhibited a more dynamic MTOC translocation toward the IS, increased F-actin polymerization upon TCR stimulation, and enhanced F-actin accumulation at the IS (**Fig. 1**). Accordingly, lamin A/C knock-down in activated primary T lymphoblasts resulted in reduced F-actin polymerization upon conjugation with APCs, further confirming that A-type lamins are required for F-actin polymerization during T cell activation.[3]

Lamin A connects the nucleus and the plasma membrane via the LINC complex (Linker of Nucleoskeleton and Cytoskeleton), which contains nesprin and SUN proteins. SUN proteins associate with lamin A and extend their domains into the perinuclear space to contact with the KASH domain of nesprins, which are located at the ONM and connect with cytoplasmic microtubules, actin, and intermediate filaments.[19] The overexpression of dominant-negative constructs of SUN1 and nesprin, which disrupt the connections between the nuclear lamina and the cytoskeleton, not only impairs F-actin polymerization upon TCR stimulation but it also prevents the increased activation of T-cells overexpressing lamin A[3] (**Fig. 1**). The connection between the LINC complex and microtubules is crucial for MTOC orientation during cell polarization and migration of fibroblasts.[20] MTOC translocation to the T cell-APC contact is essential for T cell activation,[21] and expression of A-type lamins in T cells

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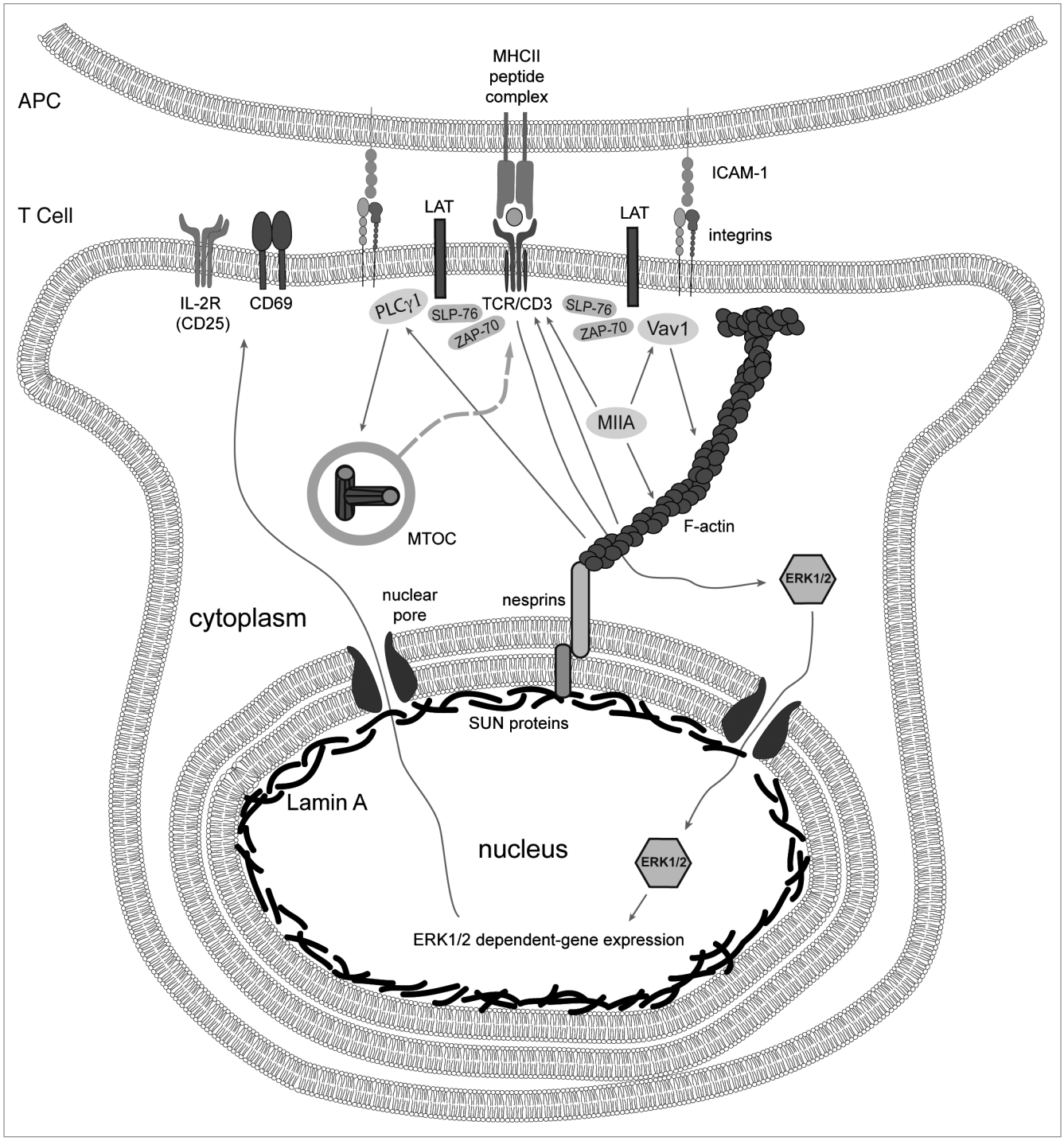

Figure 1. A-type lamins control key points of TCR-dependent increase of T-cell activation. TCR ligation results in the formation of signaling microclusters enriched in receptors and co-receptors, including the TCR and CD3, kinases and adaptor proteins that generate signaling events. A-type lamins induce an increase in TCR/CD3 clustering at the cSMAC of the IS, enhancing the phosphorylation of its downstream signaling targets. ZAP-70 (ζ-Chain-associated protein of 70 kD) associates with the TCR and phosphorylates, among other targets, LAT (linker of activated T cells) and SLP-76 (SH2 domain-containing leukocyte protein of 76 kD). Upon phosphorylation, LAT recruits PLCγ1, which induces the MTOC polarization toward the IS (discontinued arrow). Lamin A expression enhances PLCγ1 phosphorylation, accelerating MTOC translocation to the cell-cell contact. Upon phosphorylation by ZAP-70, SLP-76 binds to the guanine nucleotide exchange factor (GEF) Vav-1, which favors actin filament formation. Lamin A expression also stimulates Vav1 phosphorylation, leading to an increase in F-actin polymerization. MIIA phosphorylation is also increased by the expression of A-type lamins, contributing to both TCR/CD3 dynamic clustering at the membrane and actin polymerization. Polymerized actin modulates in turn the movement of TCR/CD3 microclusters and signaling proteins at the membrane. Expression of A-type lamins enhances ERK1/2 phosphorylation, which could be due to a TCR-dependent mechanism or to a direct interaction with Lamin A/C. A-type lamins expression in T cells promotes the gene expression of T-cell activation molecules. It increases the membrane expression of the T-cell activation molecules CD69 and CD25 (IL-2R), which is dependent on ERK1/2 phosphorylation. In the illustration, molecules are not to scale.

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accelerates MTOC repositioning toward the IS.[3] Although in cytotoxic CD8+ T cells MTOC polarization is independent on the centrosomal dissociation from the nuclear envelope,[22] it would be interesting to determine the importance of the LINC complex for MTOC translocation in APC-conjugated CD4+ T cells. Our data indicate that the physical connection between lamin A and the actin cytoskeleton through the LINC complex is essential for the optimal stimulation of T cells.

Membrane-bound adhesion molecules, such as integrins, are connected to the cytoskeleton and with the nuclear lamina through the interactions between the cytoskeleton and the LINC complex.[23,24] The connections between the nucleus and the plasma membrane are essential for the ability of the cells to sense and respond to external stimuli, converting mechanical signals into the activation of specific signaling pathways and the expression of mechanosensitive genes.[25] During T cell activation, the contact between T cells and APCs can produce mechanical signals at the membrane, which could be transmitted to the nucleus after the production of lamin A, modulating T cell functions. Accordingly, mechanotransduction has been postulated as a way of regulating T cell activation.[26] It would be interesting to determine whether lamin A regulates integrin-dependent signaling and if it regulates gene expression induced by specific mechanical forces.

The Role of Lamins in T Lymphocyte Biology

After activation, T cells proliferate and then differentiate.[27] The transient lamin A/C expression observed upon T cell activation might be essential to regulate these cellular functions. We propose that the increase in lamin A expression after T cell antigen recognition occurs in order to coordinate the process of T cell activation and that the subsequent decrease in lamin A expression would facilitate T cell proliferation and differentiation. In this sense, a low degree of differentiation and/or high levels of proliferation have been associated with a reduction in the expression of A-type lamins during homeostasis and in human malignancies, including leukemias and lymphomas.[10,28] This decrease in lamins A/C protein expression in hematological malignancies was associated with transcriptional silencing by CpG island promoter hypermethylation.[29] Also, expression of tissue specific genes during late stages of differentiation was recently related to an A-type lamins-dependent mechanism, by controlling the tethering of peripheral heterochromatin to the nuclear envelope.[30] Somatic cells displaying variable amounts of lamin A expression differ in their dynamics and efficiency during induced pluripotent stem (iPS) cell induction. The cells that express the higher amounts of lamin A display slower reprogramming and decreased efficiency during iPS cell induction.[15] Moreover, during reprogramming to iPS cells, the initially high levels of lamin A expression are reduced.[31] Consistently, in differentiated cells, lamins A/C expression is diminished by exposure of somatic cells to embryonic stem cell extracts, inducing reprogramming of gene expression for pluripotency.[32] T cell activation is also associated with important epigenetic changes in the nucleus.[31] Thus, we postulate that lamins A/C participate at least in some of the epigenetic changes that occur during immune cell activation.

Lamins A/C proteins might also be critical regulators in the coordination of T cell migration, an essential process during immune responses. In other somatic cells, nuclear repositioning during directional movement is an essential step. For example, in *Lmna*$^{-/-}$ fibroblasts, cellular migration is altered due to the disruption of the connections between the nucleus and the cytoskeleton, and as a consequence, *Lmna*$^{-/-}$ cells display delayed nuclear and MTOC reorientation during wound healing assays.[33] It would be interesting to determine whether lamin A controls the nuclear position during immune cell migration.

Lamin Expression in Other Immune Cells

During the early nineties, Rober and collaborators described the absence of lamins A/C from unstimulated hematopoietic cells from mice, as T and B lymphocytes, granulocytes, macrophages, and monocytes, either isolated from blood or bone marrow. They noted however expression of A-type lamins in certain differentiated immune cells.[7] Later on, the presence of lamins A/C mRNA and protein was observed, respectively, in human monocyte-derived dendritic cells (DCs)[34] and rat bone marrow-derived DCs.[35] Serum-free differentiation of rat and human DCs was accompanied by acquisition of lamin A/C.[36] Primary murine peritoneal macrophages and murine monocyte/macrophage-like cell line (J774A.1) express lamins A/C.[8,37] Interestingly, similarly to what we have observed upon T lymphocyte activation, stimulation of peripheral blood mononuclear cells with concanavalin A resulted in a sharpen increase in the percentage of A-type lamins expressing cells.[38] Likewise, treatment of human promyelocytic leukemia HL-60 cells with phorbol esters to trigger their differentiation into macrophage-like cells also enhances the amount of lamins A/C.[39]

On the contrary, human primary neutrophils show low-to-negligible amounts of A-type lamins,[40] and differentiation of HL-60 cells into neutrophil-like cells through stimulation with retinoic acid is accompanied by a downregulation of lamins A/C expression.[41] A-type lamins downregulation during neutrophil differentiation seems to be related to the ability of these cells to pass through the vessel walls, since lamin A overexpression in neutrophil-like HL-60 cells impairs the capacity of the cells to transit through micron-scale constrictions.[42]

Concluding Remarks

Until recently, the presence of lamins A/C in hematopoietic cells was a matter of debate. However, the importance of these proteins in the regulation of the functions of the immune system is gradually being uncovered. Another interesting subject that remains largely unexplored is the possibility that other components of the nuclear envelope could control immune

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cell functions. Regarding A-type lamins, it is becoming clearer that their expression is tightly regulated during activation and/or differentiation of immune cells. In T cells, we have recently demonstrated that although resting T lymphocytes do not express lamins A/C, their presence is observed upon antigen recognition, regulating T cell activation threshold. Other groups have observed a similar increase in lamins A/C expression in activated macrophages and DCs, while others showed that, in neutrophils, the absence of lamins A/C is crucial for the cellular ability to cross the endothelia. A-type lamins might therefore be important mediators in the coordination of physiological immune responses. Together, these evidences suggest that the amount of lamins A/C proteins could underlie some pathological conditions in the immune system.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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