T-sigcytopol - MIME 2007 Coordinator: Andres ALCOVER

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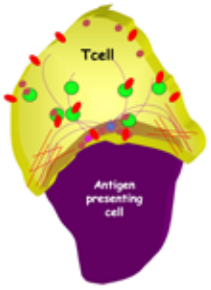
SIGNALING T CELL POLARIZATION THROUGH THE ACTIN CYTOSKELETON. From antigen recognition to virus spread

Context and goals

Acquired immune responses are initiated by T cell recognition of antigens displayed by antigen-presenting cells (APC). T cells polarize toward the APC forming a supra-molecular structure termed the **immunological synapse**, where initial triggering of signaling pathways is coordinated, thus setting up the conditions to achieve T cell responses. Interestingly, lymphotropic viruses, e.g. human T cell leukemia virus (**HTLV-1**), may subvert the mechanisms of immunological synapse formation to spread from cell to cell.

This research program had two main goals: 1) study how the immunological synapse coordinates the action of signaling proteins, cytoskeleton and vesicle traffic to control T cell responses; 2) understand how HTLV-1 exploits these mechanisms to spread from cell to cell.

Crosstalk between the signal transduction machinery and the cytoskeleton at the immune synapse



During this program we revealed that the crosstalk between the actin cytoskeleton and microtubules ensured by the membrane microfilament linker ezrin and the PDZ-containing polarity regulator Dlg1 build the architecture of the immunological synapse and control T cell antigen receptor signal transduction [1, 2].

Figure 1. *The immunological synapse is the result of intense T cell polarization*

We also demonstrated that the protein kinase HPK1 downregulates T cell activation by impairing the stability of the SLP76-GADS-LAT signaling adapter complex, *via* Ser/Thr phosphorylation of SLP76 and GADS and subsequent binding of 14-3-3 proteins [3].

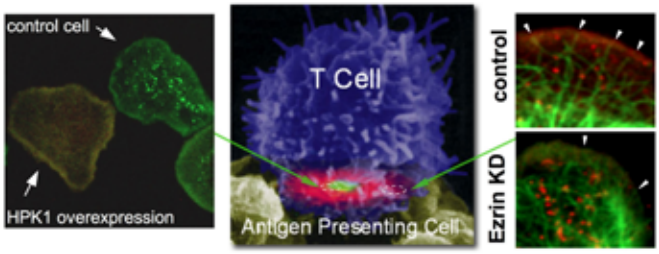


Figure 2. *Ezrin silencing perturbs microtubule organization and signaling complex topology (right) at the immunological synapse (center). HPK1 overexpression destabilizes signaling complexes at the immunological synapse (left).*

Alteration of T cell signaling and thymic development in Coronin-1A deficient mice

Analysis of genetically inactivated mice lacking the actin regulatory protein Coronin-1A (Coro-1A$^{-/-}$) showed that this protein is required for the survival, migration and antigen-specific response of T lymphocytes [4].

Microarray transcriptional analyses on thymocytes subpopulations uncovered unexpected differences. Notably, Coro-1A$^{-/-}$ CD4^{+} single positive T cells displayed gene expression profiles normally associated to the CD4CD8 double positive cell stage. Histological analyses showed reduced thymic medulla in Coro-1A$^{-/-}$ animals, further implying that Coro-1A deficiency impacts on single positive late development, prior to their egress to the periphery (Santana et al, in preparation).

'Viral biofilms' a novel mechanism for viral transmission utilized by HTLV-1

We have unveiled that HTLV-1–infected T cells transiently store viral particles as extracellular assemblies that are held together and attached to the cell surface by virally-induced extracellular matrix. Extracellular viral assemblies rapidly adhere to other cells upon cell contact, allowing virus spread and infection of target cells. Their structure, composition and function resemble those of bacterial biofilms, representing a novel mechanism for virus spread from cell to cell [5, 6, 7].

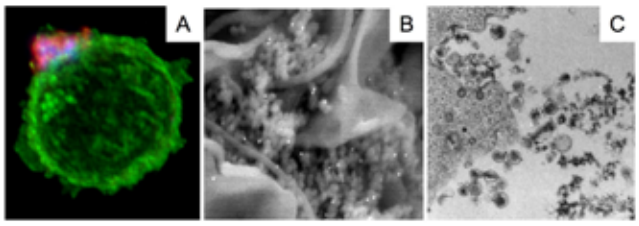


Figure 3. *'Viral Biofilm' observed by confocal microscopy (A), scanning electron microscopy (B) and transmission electron microscopy (C).*

Publications, patent

1. Lasserre et al. **EMBO J.** 2010. 29: 2301-3214.
2. Lasserre and Alcover **FEBS Lett.** 2010. 584: 4845-4850.
3. Lasserre et al. (*submitted*).
4. Mugnier et al, 2008. **PLoS One.** 3: e3467.
5. Pais-Correia et al. **Nat Med** 2010. 16: 83-90.
6. Thoulouze and Alcover. **Trends Microbiol.** 2011 (in press).
7. Alcover et al. International Patent 2010.

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