The immune system can be educated to provide one of the body’s main defence against cancer. When normal cells turn into tumour cells, some of the antigens on their surface change. T lymphocytes can recognize these new or altered antigens and are able to fight tumour through direct cytotoxicity or cytokine secretion.

Our aim is to understand the mechanisms underlying human T lymphocyte activation. We are particularly interested by the following question:

1) What is the role of the T cell cytoskeletal remodeling at the immune synapse (IS) and how is it controled?

The establishment of a T cell response requires a direct interaction between T cells and antigen presenting cells (APC). The interaction region between these cells is organized in time and space and called: the immune synapse (IS). It is characterized by a remodeling of the cytoskeleton of T cells that leads to the polarization of T cells toward the APC. We have shown this remodeling controls the directional secretion of cytokines to the IS. It is also involved in T cell activation by controlling the traffic of vesicles containing signaling molecules and the formation of signalosomes at the IS. The molecular machinery involved in this vesicular traffic is partially shared with the machinery controlling transport at the neuronal synapse. In the last few years, our group has shown that the ZAP70 kinase and its substrate LAT control the polarization of T cells toward...
actin forms a ring around the bead and IFN-γ vesicles dock around the MTOC in the middle of the synaptic zone.

the APC and that LAT trafficking to the IS depends on the SNARE protein VAMP7. We have also shown that ZAP70 controls the formation of the virological synapse, which controls HIV transmission from cell to cell.

To study these questions, we are using several approaches: high-resolution microscopy, proteomic analysis of vesicle content, T cell function analysis and several models: human silenced cells and KO mouse models.

2) How are the functions of T cells affected by their biomechanical environment?

Many cells have been shown to sense the biomechanical properties of their environment in particular the rigidity of the tissue or cells they are interacting with. T lymphocytes form IS with different APCs, which differentially induce T cell activation. Yet, the role the rigidity of these cells might play on T cell activation is unknown. We have shown that T lymphocytes sense the rigidity of the APC and adapt to these rigidities. We have recently measured the mechanical properties of different APCs by single cell rheology (collaboration with A. Asnacios, MSC, Paris-Diderot). Our results demonstrate that different APC have different rigidities and that inflammation modifies APC mechanical properties. We are now studying how the functions of T cells are affected by substrates of different rigidities.

3) How are T lymphocyte functions perturbed by pathologies?

We are studying T lymphocytes whose functions are altered by genetic hereditary mutations (primary immunodeficiencies). This approach allows us to analyze some activation mechanisms but also to better understand serious pathologies. We have characterized patients with mutations in ZAP70 and participated in the studies of patients presenting immunodeficiencies characterized by defects of Ca2+ mobilization.

We will build on our characterization of the role and control of cytoskeleton remodeling in T cell activation by analyzing at the molecular level the link existing between remodeling of the cytoskeleton, signaling and secretion. We will carry on the analysis of the biomechanical properties of APC, of how they are affected by pathologies and of the mechanosensitivity of T lymphocytes.

These studies should shed some new light on the control of T cell activation and help providing new tools to modulate immune functions.

Key publications

Year of publication 2017
Different TCR-induced T lymphocyte responses are potentiated by stiffness with variable sensitivity.

*Cite this article:* Michael Saitakis, Stéphanie Dogniaux, Christel Goudot, Nathalie Bufi, Sophie Asnacios, Mathieu Maurin, Clotilde Randriamampita, Atef Asnacios, Claire Hivroz (2017 Jun 9)

**Cross Talk between T Cells and Dendritic Cells**

**U932 - Immunity and Cancer**

*INSTITUT CURIE, 20 rue d’Ulm, 75248 Paris Cedex 05, France | 3*

**Cite this article:** Michael Saitakis, Stéphanie Dogniaux, Christel Goudot, Nathalie Bufi, Sophie Asnacios, Mathieu Maurin, Clotilde Randriamampita, Atef Asnacios, Claire Hivroz (2017 Jun 9)

**Different TCR-induced T lymphocyte responses are potentiated by stiffness with variable sensitivity.**

eLife: DOI: 10.7554/eLife.23190

**Year of publication 2013**

Paola Larghi, David J Williamson, Jean-Marie Carpier, Stéphanie Dogniaux, Karine Chemin, Armelle Bohineust, Lydia Danglot, Katharina Gaus, Thierry Galli, Claire Hivroz (2013 Feb 15)

**VAMP7 controls T cell activation by regulating the recruitment and phosphorylation of vesicular Lat at TCR-activation sites.**

*Nature immunology*: 723-31: DOI: 10.1038/ni.2609

**Year of publication 2012**

Karine Chemin, Armelle Bohineust, Stéphanie Dogniaux, Marie Tourret, Sarah Guégan, Francesc Miro, Claire Hivroz (2012 Jul 20)

**Cytokine secretion by CD4+ T cells at the immunological synapse requires Cdc42-dependent local actin remodeling but not microtubule organizing center polarity.**

*Journal of immunology (Baltimore, Md. : 1950)*: 2159-68: DOI: 10.4049/jimmunol.1200156

**Year of publication 2010**

Marie Tourret, Sarah Guégan, Karine Chemin, Stéphanie Dogniaux, Francesc Miro, Armelle Bohineust, Claire Hivroz (2010 Oct 27)

**T cell polarity at the immunological synapse is required for CD154-dependent IL-12 secretion by dendritic cells.**

*Journal of immunology (Baltimore, Md. : 1950)*: 6809-18: DOI: 10.4049/jimmunol.1001501

**Year of publication 2009**

Alain Fischer, Capucine Picard, Karine Chemin, Stéphanie Dogniaux, Françoise le Deist, Claire Hivroz (2009 Oct 16)

**ZAP70: a master regulator of adaptive immunity.**

*Seminars in immunopathology*: 107-16: DOI: 10.1007/s00281-010-0196-x