A common transcriptomic program acquired in the thymus defines tissue residency of MAIT and NKT subsets.


Résumé

Mucosal-associated invariant T (MAIT) cells are abundant T cells with unique specificity for microbial metabolites. MAIT conservation along evolution indicates important functions, but their low frequency in mice has hampered their detailed characterization. Here, we performed the first transcriptomic analysis of murine MAIT cells. MAIT1 (RORγt) and MAIT17 (RORγt) subsets were markedly distinct from mainstream T cells, but quasi-identical to NKT1 and NKT17 subsets. The expression of similar programs was further supported by strong correlations of MAIT and NKT frequencies in various organs. In both mice and humans, MAIT subsets expressed gene signatures associated with tissue residency. Accordingly, parabiosis experiments demonstrated that MAIT and NKT cells are resident in the spleen, liver, and lungs, with LFA1/ICAM1 interactions controlling MAIT1 and NKT1 retention in spleen and liver. The transcriptional program associated with tissue residency was already expressed in thymus, as confirmed by adoptive transfer experiments. Altogether, shared thymic differentiation processes generate « preset » NKT and MAIT subsets with defined effector functions, associated with specific positioning into tissues.

Anti-NKG2A mAb Is a Checkpoint Inhibitor that Promotes Anti-tumor Immunity by Unleashing Both T and NK Cells.

Cell : 1731-1743.e13 : DOI : S0092-8674(18)31322-9

Résumé

Checkpoint inhibitors have revolutionized cancer treatment. However, only a minority of patients respond to these immunotherapies. Here, we report that blocking the inhibitory NKG2A receptor enhances tumor immunity by promoting both natural killer (NK) and CD8 T cell effector functions in mice and humans. Monalizumab, a humanized anti-NKG2A antibody, enhanced NK cell activity against various tumor cells and rescued CD8 T cell function in combination with PD-x axis blockade. Monalizumab also stimulated NK cell...
activity against antibody-coated target cells. Interim results of a phase II trial of monalizumab plus cetuximab in previously treated squamous cell carcinoma of the head and neck showed a 31% objective response rate. Most common adverse events were fatigue (17%), pyrexia (13%), and headache (10%). NKG2A targeting with monalizumab is thus a novel checkpoint inhibitory mechanism promoting anti-tumor immunity by enhancing the activity of both T and NK cells, which may complement first-generation immunotherapies against cancer.


**Human genetic variants and age are the strongest predictors of humoral immune responses to common pathogens and vaccines.**

**Résumé**

Humoral immune responses to infectious agents or vaccination vary substantially among individuals, and many of the factors responsible for this variability remain to be defined. Current evidence suggests that human genetic variation influences (i) serum immunoglobulin levels, (ii) seroconversion rates, and (iii) intensity of antigen-specific immune responses. Here, we evaluated the impact of intrinsic (age and sex), environmental, and genetic factors on the variability of humoral response to common pathogens and vaccines.

Ophélie Rouxel, Jennifer DaSilva, Lucie Beaudoin, Isabelle Nel, Céline Tard, Lucie Cagninacci, Badr Kiasf, Masaya Oshima, Marc Diedisheim, Marion Salou, Alexandra Corbett, Jamie Rossjohn, James McCluskey, Raphael Scharfmann, Manuela Battaglia, Michel Polak, Olivier Lantz, Jacques Beltrand, Agnès Lehuen (2018 Jun 9)

**Author Correction: Cytotoxic and regulatory roles of mucosal-associated invariant T cells in type 1 diabetes.**
*Nature immunology* : 1035 : [DOI: 10.1038/s41590-017-0023-9](DOI: 10.1038/s41590-017-0023-9)

**Résumé**

In the version of this Article originally published, the asterisks indicating statistical significance were missing from Supplementary Figure 6; the file with the correct figure is now available.

Ruby Alonso, Héloïse Flament, Sébastien Lemoine, Christine Sedlik, Emanuel Bottasso, Isabel Pégueillet, Virginie Prémel, Jordan Denizeau, Marion Salou, Aurélie Darbois, Nicolás Gonzalo
Núñez, Benoit Salomon, David Gross, Eliane Piaggio, Olivier Lantz (2018 May 31)
**Induction of anergic or regulatory tumor-specific CD4 T cells in the tumor-draining lymph node.**
*Nature communications* : 2113 : [DOI : 10.1038/s41467-018-04524-x](https://doi.org/10.1038/s41467-018-04524-x)

**Résumé**

CD4 T cell antitumor responses have mostly been studied in transplanted tumors expressing secreted model antigens (Ags), while most mutated proteins in human cancers are not secreted. The fate of Ag-specific CD4 T cells recognizing a cytoplasmic Ag in mice bearing autochthonous tumors is still unclear. Here we show, using a genetically engineered lung adenocarcinoma mouse model, that naive tumor-specific CD4 T cells are activated and proliferate in the tumor-draining lymph node (TdLN) but do not differentiate into effectors or accumulate in tumors. Instead, these CD4 T cells are driven toward anergy or peripherally-induced Treg (pTreg) differentiation, from the early stage of tumor development. This bias toward immune suppression is restricted to the TdLN, and is maintained by Tregs enriched in the tumor Ag-specific cell population. Thus, tumors may enforce a dominant inhibition of the anti-tumor CD4 response in the TdLN by recapitulating peripheral self-tolerance mechanisms.

Année de publication : 2017

Marion Salou, Katarzyna Franciszkiewicz, Olivier Lantz (2017 Jul 28)
**MAIT cells in infectious diseases.**
*Current opinion in immunology* : 7-14 : [DOI : S0952-7915(17)30054-7](https://doi.org/S0952-7915(17)30054-7)

**Résumé**

In humans, MAIT cells represent the most abundant T cell subset reacting against bacteria. Their frequency in the blood is decreased in a large variety of infectious diseases of either bacterial or viral origin. MAIT cells accumulate at the site of bacterial infection and are protective in experimental infection models. Recent epidemiological evidence supports an implication of MAIT cells in protecting against tuberculosis. MAIT cells can be activated either through direct recognition of microbial ligands or by inflammatory cytokines such as IL-12 and IL-18. MAIT cells secrete IFN-γ, IL-17 and/or other effector molecules according to the context of triggering. MAIT cells can kill bacterially infected epithelial cells in vitro. Herein, we summarize and discuss the data suggesting a role for MAIT cells in infectious diseases.

Francois Legoux, Marion Salou, Olivier Lantz (2017 Jun 30)
**Unconventional or Preset αβ T Cells: Evolutionarily Conserved Tissue-Resident T Cells Recognizing Nonpeptidic Ligands.**
Résumé

A majority of T cells bearing the αβ T cell receptor (TCR) are specific for peptides bound to polymorphic classical major histocompatibility complex (MHC) molecules. Smaller subsets of T cells are reactive toward various nonpeptidic ligands associated with nonpolymorphic MHC class-Ib (MHC-Ib) molecules. These cells have been termed unconventional for decades, even though only the composite antigen is different from the one seen by classical T cells. Herein, we discuss the identity of these particular T cells in light of the coevolution of their TCR and MHC-Ib restricting elements. We examine their original thymic development: selection on hematopoietic cells leading to the acquisition of an original differentiation program. Most of these cells acquire memory cell features during thymic maturation and exhibit unique patterns of migration into peripheral nonlymphoid tissues to become tissue resident. Thus, these cells are termed preset T cells, as they also display a variety of effector functions. They may act as microbial or danger sentinels, fight microbes, or regulate tissue homeostasis.

Expected final online publication date for the Annual Review of Cell and Developmental Biology Volume 33 is October 6, 2017. Please see http://www.annualreviews.org/page/journal/pubdates for revised estimates.

Raymond L Barnhill, Mengliang Ye, Aude Batistella, Marc-Henri Stern, Sergio Roman-Roman, Rémi Dendale, Olivier Lantz, Sophie Piperno-Neumann, Laurence Desjardins, Nathalie Cassoux, Claire Lugassy (2017 Feb 28)
The biological and prognostic significance of angiotropism in uveal melanoma.
Laboratory investigation; a journal of technical methods and pathology : DOI: 10.1038/labinvest.2017.16

Résumé

Angiotropism is a marker of extravascular migration of melanoma cells along vascular and other structures and a prognostic factor in cutaneous melanoma. Because of this biological and prognostic importance in cutaneous melanoma, angiotropism was studied in uveal melanoma (UM). This retrospective study performed at a single ocular oncology referral center included 89 patients from the study period 2006-2008. All patients were diagnosed with UM from the choroid and/or ciliary body. All patients underwent enucleation for prognostic purposes and definitive therapy. Clinical, histopathological, and molecular variables included patient age, gender, extraocular extension, tumor location (ciliary body or not), optic nerve invasion, angiotropism, neurotropism, melanoma cell type, BAP1 mutation, and monosomy 3. Angiotropism was defined as melanoma cells arrayed along the abluminal vascular surfaces without intravasation in the sclera and/or episcleral tissue. The study included 51 women (57.3%) and 38 men with mean and median age: 63 years (range: 25-92). Mean follow-up was 4.4 years (range: 0.2 to 11). Fifty-three (59.6%) patients developed metastases and 48 (53.9%) were dead from metastases at last follow-up. Other principal variables recorded were angiotropism in 43.8%, extraocular extension in 7.9%, epithelioid/mixed cell type in 73.1%, BAP1 mutation in 41.3%, and monosomy 3 in 53.6% of cases. On multivariate analysis, extraocular extension, angiotropism, and monosomy 3 were predictive of metastasis, whereas tumor diameter, epithelioid cell type, angiotropism, and
monosomy 3 were predictive of death. Chi-square test confirmed an association between angiotropism and metastasis and death but none with BAP1 mutation and monosomy 3. In conclusion, angiotropism and monosomy 3 were independent prognostic factors for both metastases and death in UM. However, irrespective of any prognostic value, the true importance of angiotropism is its biological significance as a marker of an alternative metastatic pathway. Laboratory Investigation advance online publication, 27 February 2017; doi:10.1038/labinvest.2017.16.

Francesca Riva, Francois-Clement Bidard, Alexandre Houy, Adrien Saliou, Jordan Madic, Aurore Rampanou, Caroline Hego, Maud Milder, Paul Cottu, Marie-Paule Sabin, Anne Vincent-Salomon, Olivier Lantz, Marc-Henri Stern, Charlotte Proudhon, Jean-Yves Pierga (2017 Jan 12) 
**Patient-Specific Circulating Tumor DNA Detection during Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer.** 
*Clinical chemistry*: DOI : [clinchem.2016.262337](https://doi.org/clinchem.2016.262337)

**Résumé**

In nonmetastatic triple-negative breast cancer (TNBC) patients, we investigated whether circulating tumor DNA (ctDNA) detection can reflect the tumor response to neoadjuvant chemotherapy (NCT) and detect minimal residual disease after surgery.

**Pre-transplant donor CD4(-) invariant NKT cell expansion capacity predicts the occurrence of acute graft-versus-host disease.** 
*Leukemia*: DOI : [10.1038/leu.2016.281](https://doi.org/10.1038/leu.2016.281)

**Résumé**

Clinically useful pre-transplant predictive factors of acute graft-versus-host-disease (aGVHD) after allogeneic hematopoietic stem cell transplantation (allo-SCT) are lacking. We prospectively analyzed HSC graft content in CD34(+), NK, conventional T, regulatory T and invariant NKT (iNKT) cells in 117 adult patients before allo-SCT. Results were correlated with occurrence of aGVHD and relapse. In univariate analysis, iNKT cells were the only graft cell populations associated with occurrence of aGVHD. In multivariate analysis, CD4(-) iNKT/T cell frequency could predict grade II-IV aGVHD in bone marrow and peripheral blood stem cell (PBSC) grafts, while CD4(-) iNKT expansion capacity was predictive in PBSC grafts. ROC analyses determined the CD4(-) iNKT expansion factor as the best predictive factor of aGVHD. Incidence of grade II-IV aGVHD was reduced in patients receiving a graft with an expansion factor above versus below 6.83 (9.7 vs 80%, P<0.0001), while relapse incidence...
at two years was similar (P=0.5). The test reached 94% sensitivity and 100% specificity in the subgroup of patients transplanted with HLA 10/10 PBSCs without active disease. Analysis of this CD4(-) iNKT expansion capacity test may represent the first diagnostic tool allowing selection of the best donor to avoid severe aGVHD with preserved GVL effect after PB allo-SCT. Leukemia accepted article preview online, 14 October 2016. doi:10.1038/leu.2016.281.

Stanislas Mondot, Pierre Boudinot, Olivier Lantz (2016 Jul 10)
MAIT, MR1, microbes and riboflavin: a paradigm for the co-evolution of invariant TCRs and restricting MHCI-like molecules?
Immunogenetics

Résumé

MAIT cells express an invariant TCR that recognizes non-peptidic microbial antigens presented by the non-polymorphic MHCI-like molecule, MR1. We briefly describe how the antigens recognized by MAIT cells are generated from an unstable precursor of the riboflavin (Vitamin B2) biosynthesis pathway, as well as the main features of MAIT cells in comparison with other related T cell subsets. In silico analysis of bacterial genomes shows that the riboflavin biosynthesis pathway is highly prevalent in all groups of Prokaryotes with, however, notable exceptions. We discuss the putative functions and the evolution of the MAIT/MR1 couple: it appeared in the ancestors of mammals and is highly conserved across this group, but was independently lost in three orders. We describe the four instances of known invariant TCR and MHCI-like molecules encountered in Vertebrates. Both T cells bearing semi-invariant TCR and the associated, evolutionarily conserved MHCI-related molecules have been found in mammals or in amphibians, which suggests that other MHCI-like/invariant TCR couples might be present in other classes of Vertebrates to detect generic microbial compounds. This allows us to discuss how the recognition of riboflavin precursor derivatives by the MAIT TCR may be a way to detect invasive microbes in specific organs, and may epitomize other invariant T cell systems across vertebrates.

Katarzyna Franciszkiewicz, Marion Salou, Francois Legoux, Qian Zhou, Yue Cui, Stéphanie Bessoles, Olivier Lantz (2016 Jun 21)
MHC class I-related molecule, MR1, and mucosal-associated invariant T cells.
Immunological reviews : 120-38 : DOI : 10.1111/imr.12423

Résumé

The MHC-related 1, MR1, molecule presents a new class of microbial antigens (derivatives of the riboflavin [Vitamin B2] biosynthesis pathway) to mucosal-associated invariant T (MAIT) cells. This raises many questions regarding antigens loading and intracellular trafficking of the MR1/ligand complexes. The MR1/MAIT field is also important because MAIT cells are very abundant in humans and their frequency is modified in many infectious and non-infectious diseases. Both MR1 and the invariant TCRα chain expressed by MAIT cells are strikingly conserved among species, indicating important functions. Riboflavin is synthesized by plants
and most bacteria and yeasts but not animals, and its precursor derivatives activating MAIT cells are short-lived unless bound to MR1. The recognition of MR1 loaded with these compounds is therefore an exquisite manner to detect invasive bacteria. Herein, we provide an historical perspective of the field before describing the main characteristics of MR1, its ligands, and the few available data regarding its cellular biology. We then summarize the current knowledge of MAIT cell differentiation and discuss the definition of MAIT cells in comparison to related subsets. Finally, we describe the phenotype and effector activities of MAIT cells.

Pierre Boudinot, Stanislas Mondot, Luc Jouneau, Luc Teyton, Marie-Paule Lefranc, Olivier Lantz (2016 May 13)
Restricting nonclassical MHC genes coevolve with TRAV genes used by innate-like T cells in mammals.

Résumé

Whereas major histocompatibility class-1 (MH1) proteins present peptides to T cells displaying a large T-cell receptor (TR) repertoire, MH1Like proteins, such as CD1D and MR1, present glycolipids and microbial riboflavin precursor derivatives, respectively, to T cells expressing invariant TR-α (iTRA) chains. The groove of such MH1Like, as well as iTRA chains used by mucosal-associated invariant T (MAIT) and natural killer T (NKT) cells, respectively, may result from a coevolution under particular selection pressures. Herein, we investigated the evolutionary patterns of the iTRA of MAIT and NKT cells and restricting MH1Like proteins: MR1 appeared 170 Mya and is highly conserved across mammals, evolving more slowly than other MH1Like. It has been pseudogenized or independently lost three times in carnivores, the armadillo, and lagomorphs. The corresponding TRAV1 gene also evolved slowly and harbors highly conserved complementarity determining regions 1 and 2. TRAV1 is absent exclusively from species in which MR1 is lacking, suggesting that its loss released the purifying selection on MR1. In the rabbit, which has very few NKT and no MAIT cells, a previously unrecognized iTRA was identified by sequencing leukocyte RNA. This iTRA uses TRAV41, which is highly conserved across several groups of mammals. A rabbit MH1Like gene was found that appeared with mammals and is highly conserved. It was independently lost in a few groups in which MR1 is present, like primates and Muridae, illustrating compensatory emergences of new MH1Like/Invariant T-cell combinations during evolution. Deciphering their role is warranted to search similar effector functions in humans.

Francesca Riva, Oleksii I Dronov, Dmytro I Khomenko, Florence Huguet, Christophe Louvet, Pascale Mariani, Marc-Henri Stern, Olivier Lantz, Charlotte Proudhon, Jean-Yves Pierga, Francois-Clement Bidard (2016 Feb 10)
Clinical applications of circulating tumor DNA and circulating tumor cells in pancreatic cancer.
Molecular oncology : 481-93 : DOI : 10.1016/j.molonc.2016.01.006

Résumé

Pancreatic ductal adenocarcinoma (PDAC) is the most frequent pancreatic cancer type and is characterized by a dismal prognosis due to late diagnosis, local tumor invasion, frequent distant metastases and poor sensitivity to current therapy. In this context, circulating tumor cells and circulating tumor DNA constitute easily accessible blood-borne tumor biomarkers that may prove their clinical interest for screening, early diagnosis and metastatic risk assessment of PDAC. Moreover these markers represent a tool to assess PDAC mutational landscape. In this review, together with key biological findings, we summarize the clinical results obtained using « liquid biopsies » at the different stages of the disease, for early and metastatic diagnosis as well as monitoring during therapy.

Année de publication : 2015

Nabil Amirouchene-Angelozzi, Marie Schoumacher, Marc-Henri Stern, Nathalie Cassoux, Laurence Desjardins, Sophie Piperno-Neumann, Olivier Lantz, Sergio Roman-Roman (2015 Dec 24)

Upcoming translational challenges for uveal melanoma.
British journal of cancer : 1746 : DOI : 10.1038/bjc.2015.456

Résumé