Année de publication : 2015

Zhijian J Chen, Sebastian Amigorena (2015 Feb 12)
Editorial overview: innate immunity.
Current opinion in immunology : v-vi : DOI : 10.1016/j.coi.2015.01.016

Résumé

Année de publication : 2014

Miranda L Broz, Mikhail Binnewies, Bijan Boldajipour, Amanda E Nelson, Joshua L Pollack, David J Erle, Andrea Barczak, Michael D Rosenblum, Adil Daud, Diane L Barber, Sebastian Amigorena, Laura J Van't Veer, Anne I Sperling, Denise M Wolf, Matthew F Krummel (2014 Dec 3)
Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity.
Cancer cell : 638-52 : DOI : 10.1016/j.ccell.2014.09.007

Résumé

It is well understood that antigen-presenting cells (APCs) within tumors typically do not maintain cytotoxic T cell (CTL) function, despite engaging them. Across multiple mouse tumor models and human tumor biopsies, we have delineated the intratumoral dendritic cell (DC) populations as distinct from macrophage populations. Within these, CD103(+) DCs are extremely sparse and yet remarkably capable CTL stimulators. These are uniquely dependent on IRF8, Zbtb46, and Batf3 transcription factors and are generated by GM-CSF and FLT3L cytokines. Regressing tumors have higher proportions of these cells, T-cell-dependent immune clearance relies on them, and abundance of their transcripts in human tumors correlates with clinical outcome. This cell type presents opportunities for prognostic and therapeutic approaches across multiple cancer types.

Adriana R Mantegazza, Allison L Zajac, Alison Twelvetrees, Erika L F Holzbaur, Sebastián Amigorena, Michael S Marks (2014 Oct 15)
TLR-dependent phagosome tubulation in dendritic cells promotes phagosome cross-talk to optimize MHC-II antigen presentation.
Proceedings of the National Academy of Sciences of the United States of America : 15508-13 : DOI : 10.1073/pnas.1412998111

Résumé

Dendritic cells (DCs) phagocytose large particles like bacteria at sites of infection and progressively degrade them within maturing phagosomes. Phagosomes in DCs are also signaling platforms for pattern recognition receptors, such as Toll-like receptors (TLRs), and sites for assembly of cargo-derived peptides with major histocompatibility complex class II

(MHC-II) molecules. Although TLR signaling from phagosomes stimulates presentation of phagocytosed antigens, the mechanisms underlying this enhancement and the cell surface delivery of MHC-II-peptide complexes from phagosomes are not known. We show that in DCs, maturing phagosomes extend numerous long tubules several hours after phagocytosis. Tubule formation requires an intact microtubule and actin cytoskeleton and MyD88-dependent phagosomal TLR signaling, but not phagolysosome formation or extensive proteolysis. In contrast to the tubules that emerge from endolysosomes after uptake of soluble ligands and TLR stimulation, the late-onset phagosomal tubules are not essential for delivery of phagosome-derived MHC-II-peptide complexes to the plasma membrane. Rather, tubulation promotes MHC-II presentation by enabling maximal cargo transfer among phagosomes that bear a TLR signature. Our data show that phagosomal tubules in DCs are functionally distinct from those that emerge from lysosomes and are unique adaptations of the phagocytic machinery that facilitate cargo exchange and antigen presentation among TLR-signaling phagosomes.

Elodie Segura, Sebastian Amigorena (2014 Jan 30)
[Inflammatory dendritic cells].
Médecine sciences : M/S : 64-8 : DOI : 10.1051/medsci/20143001015

Résumé

Dendritic cells are a rare and heterogeneous population of professional antigen-presenting cells. Several murine dendritic cell subpopulations have been identified that differ in their phenotype and functional properties. In the steady state, committed dendritic cell precursors differentiate into lymphoid organ-resident dendritic cells and migratory tissue dendritic cells. During inflammation appears an additional dendritic cell subpopulation that has been termed « inflammatory dendritic cells ». Inflammatory dendritic cells differentiate in situ from monocytes recruited to the site of inflammation. Here, we discuss how mouse inflammatory dendritic cells differ from macrophages and from other dendritic cell populations. Finally, we review recent work on human inflammatory dendritic cells.

Année de publication : 2013

Elodie Segura, Sebastian Amigorena (2013 Dec 17)
Cross-presentation by human dendritic cell subsets.
Immunology letters : 73-8 : DOI : 10.1016/j.imlet.2013.12.001

Résumé

Dendritic cells (DCs) are a heterogeneous population of professional antigen-presenting cells. Several murine DC subsets differ in their phenotype and functional properties, in particular in their ability to cross-present antigens (i.e. to present exogenous antigens on their MHC class I molecules). In humans, distinct DC subpopulations have also been identified but whether some human DC subsets are also specialized at cross-presentation remains debated. Here we review the DC subsets that have been identified in humans and we discuss recent work

that addresses their ability to cross-present antigens and their efficiency for CD8(+) T cells activation.

Elodie Segura, Sebastian Amigorena (2013 Jul 9)
Inflammatory dendritic cells in mice and humans.
Trends in immunology : 440-5 : DOI : 10.1016/j.it.2013.06.001

Résumé

Dendritic cells (DCs) are a heterogeneous population of professional antigen-presenting cells. Several murine DC subsets have been identified that differ in their phenotype and functional properties. In the steady state, DC precursors originating from the bone marrow give rise to lymphoid-organ-resident DCs and to migratory tissue DCs. During inflammation, an additional DC subset has been described, so-called inflammatory DCs (infDCs), which differentiate from monocytes recruited to the site of inflammation. Here, we review recent work on the development and functions of murine infDCs. We also examine the criteria that define infDCs. Finally, we discuss the characterization of human infDCs and their potential role in inflammatory diseases.

Elodie Segura, Sebastian Amigorena (2013 Jun 14)
Identification of human inflammatory dendritic cells.
Oncoimmunology : e23851

Résumé

Dendritic cells (DCs) are professional antigen-presenting cells that comprise several subsets with distinct phenotypes and functions, including inflammatory DCs that appear during inflammation. By analyzing human inflammatory fluids (arthritic synovial fluid and tumor ascites), we have identified the human equivalent of inflammatory DCs.

Elodie Segura, Mélanie Durand, Sebastian Amigorena (2013 Apr 10)
Similar antigen cross-presentation capacity and phagocytic functions in all freshly isolated human lymphoid organ-resident dendritic cells.
The Journal of experimental medicine : 1035-47 : DOI : 10.1084/jem.20121103

Résumé

Dendritic cells (DCs) represent a heterogeneous population of antigen-presenting cells that initiate and orient immune responses in secondary lymphoid organs. In mice, lymphoid organ-resident CD8(+) DCs are specialized at cross-presentation and have developed specific adaptations of their endocytic pathway (high pH, low degradation, and high export to the cytosol). In humans, blood BDCA3(+) DCs were recently shown to be the homologues of mouse CD8(+) DCs. They were also proposed to cross-present antigens more efficiently than

other blood DC subsets after in vitro activation, suggesting that in humans cross-presentation is restricted to certain DC subsets. The DCs that cross-present antigen physiologically, however, are the ones present in lymphoid organs. Here, we show that freshly isolated tonsil-resident BDCA1(+) DCs, BDCA3(+) DCs, and pDCs all cross-present soluble antigen efficiently, as compared to macrophages, in the absence of activation. In addition, BDCA1(+) and BDCA3(+) DCs display similar phagosomal pH and similar production of reactive oxygen species in their phagosomes. All three DC subsets, in contrast to macrophages, also efficiently export internalized proteins to the cytosol. We conclude that all freshly isolated lymphoid organ-resident human DCs, but not macrophages, display high intrinsic cross-presentation capacity.

Alexandre Boissonnas, Fabrice Licata, Lucie Poupel, Sébastien Jacquelin, Luc Fetler, Sophie Krumeich, Clotilde Théry, Sébastian Amigorena, Christophe Combadière (2013 Jan 30)
CD8+ tumor-infiltrating T cells are trapped in the tumor-dendritic cell network.
Neoplasia (New York, N.Y.) : 85-94

Résumé

Chemotherapy enhances the antitumor adaptive immune T cell response, but the immunosuppressive tumor environment often dominates, resulting in cancer relapse. Antigen-presenting cells such as tumor-associated macrophages (TAMs) and tumor dendritic cells (TuDCs) are the main protagonists of tumor-infiltrating lymphocyte (TIL) immunosuppression. TAMs have been widely investigated and are associated with poor prognosis, but the immunosuppressive activity of TuDCs is less well understood. We performed two-photon imaging of the tumor tissue to examine the spatiotemporal interactions between TILs and TuDCs after chemotherapy. In a strongly immunosuppressive murine tumor model, cyclophosphamide-mediated chemotherapy transiently enhanced the antitumor activity of adoptively transferred ovalbumin-specific CD8(+) T cell receptor transgenic T cells (OTI) but barely affected TuDC compartment within the tumor. Time lapse imaging of living tumor tissue showed that TuDCs are organized as a mesh with dynamic interconnections. Once infiltrated into the tumor parenchyma, OTI T cells make antigen-specific and long-lasting contacts with TuDCs. Extensive analysis of TIL infiltration on histologic section revealed that after chemotherapy the majority of OTI T cells interact with TuDCs and that infiltration is restricted to TuDC-rich areas. We propose that the TuDC network exerts antigen-dependent unproductive retention that trap T cells and limit their antitumor effectiveness.

Année de publication : 2012

Adriana R Mantegazza, Joao G Magalhaes, Sebastian Amigorena, Michael S Marks (2012 Nov 7)
Presentation of phagocytosed antigens by MHC class I and II.
Traffic (Copenhagen, Denmark) : 135-52 : DOI : 10.1111/tra.12026

Résumé

Phagocytosis provides innate immune cells with a mechanism to take up and destroy pathogenic bacteria, apoptotic cells and other large particles. In some cases, however, peptide antigens from these particles are preserved for presentation in association with major histocompatibility complex (MHC) class I or class II molecules in order to stimulate antigen-specific T cells. Processing and presentation of antigens from phagosomes presents a number of distinct challenges relative to antigens internalized by other means; while bacterial antigens were among the first discovered to be presented to T cells, analyses of the cellular mechanisms by which peptides from phagocytosed antigens assemble with MHC molecules and by which these complexes are then expressed at the plasma membrane have lagged behind those of conventional model soluble antigens. In this review, we cover recent advances in our understanding of these processes, including the unique cross-presentation of phagocytosed antigens by MHC class I molecules, and in their control by signaling modalities in phagocytic cells.

Luigia Pace, Andy Tempez, Catharina Arnold-Schrauf, Fabrice Lemaitre, Philippe Bousso, Luc Fetler, Tim Sparwasser, Sebastian Amigorena (2012 Nov 1)

Regulatory T cells increase the avidity of primary CD8+ T cell responses and promote memory.

Science (New York, N.Y.) : 532-6 : DOI : 10.1126/science.1227049

Résumé

Although regulatory T cells (T(regs)) are known to suppress self-reactive autoimmune responses, their role during T cell responses to nonself antigens is not well understood. We show that T(regs) play a critical role during the priming of immune responses in mice. T(reg) depletion induced the activation and expansion of a population of low-avidity CD8(+) T cells because of overproduction of CCL-3/4/5 chemokines, which stabilized the interactions between antigen-presenting dendritic cells and low-avidity T cells. In the absence of T(regs), the avidity of the primary immune response was impaired, which resulted in reduced memory to Listeria monocytogenes. These results suggest that T(regs) are important regulators of the homeostasis of CD8(+) T cell priming and play a critical role in the induction of high-avidity primary responses and effective memory.

Eik Hoffmann, Fiorella Kotsias, Géraldine Visentin, Pierre Bruhns, Ariel Savina, Sebastian Amigorena (2012 Aug 22)

Autonomous phagosomal degradation and antigen presentation in dendritic cells.

Proceedings of the National Academy of Sciences of the United States of America : 14556-61 : DOI : 10.1073/pnas.1203912109

Résumé

Phagocytosis plays a critical role in both innate and adaptive immunity. Phagosomal fusion

with late endosomes and lysosomes enhances proteolysis, causing degradation of the phagocytic content. Increased degradation participates in both innate protection against pathogens and the production of antigenic peptides for presentation to T lymphocytes during adaptive immune responses. Specific ligands present in the phagosomal cargo influence the rate of phagosome fusion with lysosomes, thereby modulating both antigen degradation and presentation. Using a combination of cell sorting techniques and single phagosome flow cytometry-based analysis, we found that opsonization with IgG accelerates antigen degradation within individual IgG-containing phagosomes, but not in other phagosomes present in the same cell and devoid of IgG. Likewise, IgG opsonization enhances antigen presentation to CD4(+) T lymphocytes only when antigen and IgG are present within the same phagosome, whereas cells containing phagosomes with either antigen or IgG alone failed to present antigen efficiently. Therefore, individual phagosomes behave autonomously, in terms of both cargo degradation and antigen presentation to CD4(+) T cells. Phagosomal autonomy could serve as a basis for the intracellular discrimination between self and nonself antigens, resulting in the preferential presentation of peptides derived from opsonized, nonself antigens.

Fiorella Kotsias, Eik Hoffmann, Sebastian Amigorena, Ariel Savina (2012 Jul 26)
Reactive oxygen species production in the phagosome: impact on antigen presentation in dendritic cells.
Antioxidants & redox signaling : 714-29 : DOI : 10.1089/ars.2012.4557

Résumé

The NADPH oxidase 2 (NOX2) is known to play a major role in innate immunity for several decades. Phagocytic cells provide host defense by ingesting microbes and destroy them by different mechanisms, including the generation of reactive oxygen species (ROS) by NOX2, a process known as oxidative burst. The phagocytic pathway of dendritic cells (DCs), highly adapted to antigen processing, has been shown to display remarkable differences compared to other phagocytes. Contrary to macrophages and neutrophils, the main function of DC phagosomes is antigen presentation rather than pathogen killing or clearance of cell debris.

Olivier P Joffre, Elodie Segura, Ariel Savina, Sebastian Amigorena (2012 Jul 13)
Cross-presentation by dendritic cells.
Nature reviews. Immunology : 557-69 : DOI : 10.1038/nri3254

Résumé

The presentation of exogenous antigens on MHC class I molecules, known as cross-presentation, is essential for the initiation of CD8(+) T cell responses. In vivo, cross-presentation is mainly carried out by specific dendritic cell (DC) subsets through an adaptation of their endocytic and phagocytic pathways. Here, we summarize recent advances in our understanding of the intracellular mechanisms of cross-presentation and discuss its role in immunity and tolerance in the context of specialization between DC subsets. Finally, we review current strategies to use cross-presentation for immunotherapy.

Pascale Hubert, Sebastian Amigorena (2012 Jun 22)

Antibody-dependent cell cytotoxicity in monoclonal antibody-mediated tumor immunotherapy.

Oncoimmunology : 103-105

Résumé

Antibody-dependent cell cytotoxicity (ADCC) is critical in monoclonal antibody (mAb)-mediated cancer therapy. We recently showed that a tumor-specific mAb in combination with cyclophosphamide inhibited tumor cell growth and induced ADCC-synapses between tumor and effector cells in vivo, opening perspectives to enhance anti-tumor responses by manipulating the immune system.