Année de publication : 2020

Marianne Burbage, Sebastian Amigorena (2020 Aug 14)
A dendritic cell multitasks to tackle cancer.
Nature : 533-534 : DOI : 10.1038/d41586-020-02339-9

Résumé

Patrycja Kozik, Marine Gros, Daniel N Itzhak, Leonel Joannas, Sandrine Heurtebise-Chrétien, Patrycja A Krawczyk, Pablo Rodríguez-Silvestre, Andrés Alloatti, Joao Gamelas Magalhaes, Elaine Del Nery, Georg H H Borner, Sebastian Amigorena (2020 Jul 16)
Small Molecule Enhancers of Endosome-to-Cytosol Import Augment Anti-tumor Immunity.
Cell reports : 107905 : DOI : S2211-1247(20)30886-X

Résumé

Cross-presentation of antigens by dendritic cells (DCs) is critical for initiation of anti-tumor immune responses. Yet, key steps involved in trafficking of antigens taken up by DCs remain incompletely understood. Here, we screen 700 US Food and Drug Administration (FDA)-approved drugs and identify 37 enhancers of antigen import from endolysosomes into the cytosol. To reveal their mechanism of action, we generate proteomic organellar maps of control and drug-treated DCs (focusing on two compounds, prazosin and tamoxifen). By combining organellar mapping, quantitative proteomics, and microscopy, we conclude that import enhancers undergo lysosomal trapping leading to membrane permeation and antigen release. Enhancing antigen import facilitates cross-presentation of soluble and cell-associated antigens. Systemic administration of prazosin leads to reduced growth of MC38 tumors and to a synergistic effect with checkpoint immunotherapy in a melanoma model. Thus, inefficient antigen import into the cytosol limits antigen cross-presentation, restraining the potency of anti-tumor immune responses and efficacy of checkpoint blockers.

Nicolas Gonzalo Núñez, Jimena Tosello Boari, Rodrigo Nalio Ramos, Wilfrid Richer, Nicolas Cagnard, Cyrill Dimitri Anderfuhren, Leticia Laura Niborski, Jeremy Bigot, Didier Meseure, Philippe De La Rochere, Maud Milder, Sophie Viel, Delphine Loirat, Louis Pérol, Anne Vincent-Salomon, Xavier Sastre-Garau, Becher Burkhard, Christine Sedlik, Olivier Lantz, Sebastian Amigorena, Eliane Piaggio (2020 Jul 1)
Tumor invasion in draining lymph nodes is associated with Treg accumulation in breast cancer patients.
Nature communications : 3272 : DOI : 10.1038/s41467-020-17046-2

Résumé

Tumor-draining lymph node (TDLN) invasion by metastatic cells in breast cancer correlates with poor prognosis and is associated with local immunosuppression, which can be partly mediated by regulatory T cells (Tregs). Here, we study Tregs from matched tumor-invaded and non-invaded TDLNs, and breast tumors. We observe that Treg frequencies increase with nodal invasion, and that Tregs express higher levels of co-inhibitory/stimulatory receptors than effector cells. Also, while Tregs show conserved suppressive function in TDLN and tumor, conventional T cells (Tconvs) in TDLNs proliferate and produce Th1-inflammatory cytokines, but are dysfunctional in the tumor. We describe a common transcriptomic signature shared by Tregs from tumors and nodes, including CD80, which is significantly associated with poor patient survival. TCR RNA-sequencing analysis indicates trafficking between TDLNs and tumors and ongoing Tconv/Treg conversion. Overall, TDLN Tregs are functional and express a distinct pattern of druggable co-receptors, highlighting their potential as targets for cancer immunotherapy.

Fernando Erra Díaz, Valeria Ochoa, Antonela Merlotti, Ezequiel Dantas, Ignacio Mazzitelli, Virginia Gonzalez Polo, Juan Sabatté, Sebastián Amigorena, Elodie Segura, Jorge Geffner (2020 May 7)
Extracellular Acidosis and mTOR Inhibition Drive the Differentiation of Human Monocyte-Derived Dendritic Cells.
Cell reports : 107613 : DOI : S2211-1247(20)30562-3

Résumé

During inflammation, recruited monocytes can differentiate either into macrophages or dendritic cells (DCs); however, little is known about the environmental factors that determine this cell fate decision. Low extracellular pH is a hallmark of a variety of inflammatory processes and solid tumors. Here, we report that low pH dramatically promotes the differentiation of monocytes into DCs (monocyte-derived DCs [mo-DCs]). This process is associated with a reduction in glucose consumption and lactate production, the upregulation of mitochondrial respiratory chain genes, and the inhibition of mTORC1 activity. Interestingly, we also find that both serum starvation and pharmacological inhibition of mTORC1 markedly promote the differentiation of mo-DCs. Our study contributes to better understanding the mechanisms that govern the differentiation of monocytes into DCs and reveals the role of both extracellular pH and mTORC1 as master regulators of monocyte cell fate.

Sandrine Moutel, Anne Beugnet, Aurélie Schneider, Bérangère Lombard, Damarys Loew, Sebastian Amigorena, Franck Perez, Elodie Segura (2020 Apr 1)
Surface LSP-1 Is a Phenotypic Marker Distinguishing Human Classical versus Monocyte-Derived Dendritic Cells.
iScience : 100987 : DOI : S2589-0042(20)30171-1

Résumé

Human mononuclear phagocytes comprise several subsets of dendritic cells (DCs),

monocytes, and macrophages. Distinguishing one population from another is challenging, especially in inflamed tissues, owing to the promiscuous expression of phenotypic markers. Using a synthetic library of humanized llama single domain antibodies, we identified a novel surface marker for human naturally occurring monocyte-derived DCs. Our antibody targets an extra-cellular domain of LSP-1, specifically on monocyte-derived DCs, but not on other leukocytes, in particular monocytes, macrophages, classical DCs, or the recently described blood DC3 population. Our findings will pave the way for a better characterization of human mononuclear phagocytes in pathological settings.

Audrey Bellesoeur, Nouritza Torossian, Sebastian Amigorena, Emanuela Romano (2020 Mar 29)
Advances in theranostic biomarkers for tumor immunotherapy.
Current opinion in chemical biology : 79-90 : DOI : S1367-5931(20)30021-1

Résumé

Cancer treatment has known a revolution with the emergence of immune checkpoint inhibitors. However, accurate theranostic biomarkers are lacking. In this review, we discuss different types of biomarkers currently under investigation. First, we focus on tissue biomarkers including PD-L1 expression by immunohistochemistry-the first Food and Drug Administration-approved biomarker-despite conflicting results. In addition, we report on novel biomarkers, including protein-based, molecular (tumor mutational load, immune signature…), circulating (neutrophil-to-lymphocyte ratio, serum cytokines…), and imaging-based biomarkers (radiomic signatures and positron-emission tomography using radiolabeled antibodies). We highlight the limitations of each candidate biomarker and finally discuss combinatorial approaches for their use and the opportunity to switch from a predictive strategy of biomarker research to an adaptive one in the field of cancer immunotherapy.

Mengliang Ye, Christel Goudot, Thomas Hoyler, Benjamin Lemoine, Sebastian Amigorena, Elina Zueva (2020 Mar 21)
Specific subfamilies of transposable elements contribute to different domains of T lymphocyte enhancers.
Proceedings of the National Academy of Sciences of the United States of America : 7905-7916 : DOI : 10.1073/pnas.1912008117

Résumé

Transposable elements (TEs) compose nearly half of mammalian genomes and provide building blocks for -regulatory elements. Using high-throughput sequencing, we show that 84 TE subfamilies are overrepresented, and distributed in a lineage-specific fashion in core and boundary domains of CD8 T cell enhancers. Endogenous retroviruses are most significantly enriched in core domains with accessible chromatin, and bear recognition motifs for immune-related transcription factors. In contrast, short interspersed elements (SINEs) are preferentially overrepresented in nucleosome-containing boundaries. A substantial proportion of these SINEs harbor a high density of the enhancer-specific histone mark

H3K4me1 and carry sequences that match enhancer boundary nucleotide composition. Motifs with regulatory features are better preserved within enhancer-enriched TE copies compared to their subfamily equivalents located in gene deserts. TE-rich and TE-poor enhancers associate with both shared and unique gene groups and are enriched in overlapping functions related to lymphocyte and leukocyte biology. The majority of T cell enhancers are shared with other immune lineages and are accessible in common hematopoietic progenitors. A higher proportion of immune tissue-specific enhancers are TE-rich compared to enhancers specific to other tissues, correlating with higher TE occurrence in immune gene-associated genomic regions. Our results suggest that during evolution, TEs abundant in these regions and carrying motifs potentially beneficial for enhancer architecture and immune functions were particularly frequently incorporated by evolving enhancers. Their putative selection and regulatory cooption may have accelerated the evolution of immune regulatory networks.

Luigia Pace, Sebastian Amigorena (2020 Feb 18)
Epigenetics of T cell fate decision.
Current opinion in immunology : 43-50 : DOI : S0952-7915(20)30002-9

Résumé

The changes of transcription factor activity and chromatin dynamics guide functional differentiation of T cell subsets, including commitment to short-lived effectors and long-term survival of memory T cells. Understanding the lineage relationships among the different stages of effector and memory differentiation has profound therapeutic implications for the development of new vaccine and immunotherapy protocols. Here we review the contribution of chromatin architecture to T cell specification, focusing on the interplay between epigenetic changes and transcriptional programs linked to T cell plasticity, commitment and memory. We will also discuss the translational implications of epigenetic control in the context of infections and cancer.

Année de publication : 2019

Gehrmann U1,2, Burbage M3, Zueva E3, Goudot C3, Esnault C4, Ye M3, Carpier JM3, Burgdorf N3, Hoyler T3, Suarez G3, Joannas L3, Heurtebise-Chrétien S3, Durand S5,6, Panes R7,8, Bellemare-Pelletier A8, Sáez PJ3, Aprahamian F5,6, Lefevre D5,6, Adoue V9, Zine El Aabidine A4, Muhammad Ahmad M4, Hivroz C3, Joffre O10, Cammas F11,12, Kroemer G5,6,13,14,15, Gagnon E7,8, Andrau JC4, Amigorena S1. (2019 Dec 17)
Critical role for TRIM28 and HP1β/γ in the epigenetic control of T cell metabolic reprograming and effector differentiation.
Proceedings of the National Academy of Sciences : 116 : Proc Natl Acad Sci U S A. 2019 Dec 17;116(51):25839-25849. doi: 10.1073/pnas.1901639116. Epub 2019 Nov 27. : 25839,25849 : DOI : 10.1073/pnas.1901639116

Résumé

Naive $CD4^+$ T lymphocytes differentiate into different effector types, including helper and regulatory cells (Th and Treg, respectively). Heritable gene expression programs that define these effector types are established during differentiation, but little is known about the epigenetic mechanisms that install and maintain these programs. Here, we use mice defective for different components of heterochromatin-dependent gene silencing to investigate the epigenetic control of $CD4^+$ T cell plasticity. We show that, upon T cell receptor (TCR) engagement, naive and regulatory T cells defective for TRIM28 (an epigenetic adaptor for histone binding modules) or for heterochromatin protein 1 β and γ isoforms (HP1β/γ, 2 histone-binding factors involved in gene silencing) fail to effectively signal through the PI3K-AKT-mTOR axis and switch to glycolysis. While differentiation of naive $TRIM28^{-/-}$ T cells into cytokine-producing effector T cells is impaired, resulting in reduced induction of autoimmune colitis, $TRIM28^{-/-}$ regulatory T cells also fail to expand in vivo and to suppress autoimmunity effectively. Using a combination of transcriptome and chromatin immunoprecipitation-sequencing (ChIP-seq) analyses for H3K9me3, H3K9Ac, and RNA polymerase II, we show that reduced effector differentiation correlates with impaired transcriptional silencing at distal regulatory regions of a defined set of Treg-associated genes, including, for example, NRP1 or Snai3. We conclude that TRIM28 and HP1β/γ control metabolic reprograming through epigenetic silencing of a defined set of Treg-characteristic genes, thus allowing effective T cell expansion and differentiation into helper and regulatory phenotypes.

Kondratova M1, Czerwinska U1,2, Sompairac N1,2, Amigorena SD3, Soumelis V3, Barillot E1, Zinovyev A1, Kuperstein I4. (2019 Oct 22)

A multiscale signalling network map of innate immune response in cancer reveals cell heterogeneity signatures.

Nature communications : 10 : Nat Commun. 2019 Oct 22;10(1):4808. doi: 10.1038/s41467-019-12270-x. : 4808 : DOI : 10.1038/s41467-019-12270-x

Résumé

The lack of integrated resources depicting the complexity of the innate immune response in cancer represents a bottleneck for high-throughput data interpretation. To address this challenge, we perform a systematic manual literature mining of molecular mechanisms governing the innate immune response in cancer and represent it as a signalling network map. The cell-type specific signalling maps of macrophages, dendritic cells, myeloid-derived suppressor cells and natural killers are constructed and integrated into a comprehensive meta map of the innate immune response in cancer. The meta-map contains 1466 chemical species as nodes connected by 1084 biochemical reactions, and it is supported by information from 820 articles. The resource helps to interpret single cell RNA-Seq data from macrophages and natural killer cells in metastatic melanoma that reveal different anti- or pro-tumor sub-populations within each cell type. Here, we report a new open source analytic platform that supports data visualisation and interpretation of tumour microenvironment activity in cancer.

Année de publication : 2017

Goudot C1, Coillard A1, Villani AC2, Gueguen P1, Cros A1, Sarkizova S3, Tang-Huau TL4, Bohec M5, Baulande S5, Hacohen N2, Amigorena S1, Segura E6. (2019 Sep 19)

Aryl Hydrocarbon Receptor Controls Monocyte Differentiation into Dendritic Cells versus Macrophages.

Immunity : 47 : Immunity. 2017 Sep 19;47(3):582-596.e6. doi: 10.1016/j.immuni.2017.08.016. : 582,596 : DOI : 10.1016/j.immuni.2017.08.016

Résumé

After entering tissues, monocytes differentiate into cells that share functional features with either macrophages or dendritic cells (DCs). How monocyte fate is directed toward monocyte-derived macrophages (mo-Macs) or monocyte-derived DCs (mo-DCs) and which transcription factors control these differentiation pathways remains unknown. Using an in vitro culture model yielding human mo-DCs and mo-Macs closely resembling those found in vivo in ascites, we show that IRF4 and MAFB were critical regulators of monocyte differentiation into mo-DCs and mo-Macs, respectively. Activation of the aryl hydrocarbon receptor (AHR) promoted mo-DC differentiation through the induction of BLIMP-1, while impairing differentiation into mo-Macs. AhR deficiency also impaired the in vivo differentiation of mouse mo-DCs. Finally, AHR activation correlated with mo-DC infiltration in leprosy lesions. These results establish that mo-DCs and mo-Macs are controlled by distinct transcription factors and show that AHR acts as a molecular switch for monocyte fate specification in response to micro-environmental factors.

Année de publication : 2019

Antonela Merlotti, Alvaro López Malizia, Paula Michea, Pierre-Emmanuel Bonte, Christel Goudot, María Sol Carregal, Nicolás Nuñez, Christine Sedlik, Ana Ceballos, Vassili Soumelis, Sebastián Amigorena, Jorge Geffner, Eliane Piaggio, Juan Sabatte (2019 Aug 21)

Aberrant fucosylation enables breast cancer clusterin to interact with dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN).

Oncoimmunology : e1629257 : DOI : 10.1080/2162402X.2019.1629257

Résumé

Clusterin is a glycoprotein able to mediate different physiological functions such as control of complement activation, promotion of unfolded protein clearance and modulation of cell survival. Clusterin is overexpressed in many types of cancers and a large body of evidence suggests that it promotes carcinogenesis and tumor progression. We have previously described a novel clusterin glycoform present in human semen, but not in serum, highly enriched in terminal fucose motifs. Here we show that human luminal breast cancer (LBC) clusterin also bears terminal fucosylated glycans, conferring clusterin the ability to interact with DC-SIGN, a C-type lectin receptor expressed by myeloid cells. This clusterin glycosylation pattern was absent or diminished in non-involved juxtatumoral tissue,

suggesting that fucosylated clusterin might represent a cancer associated glycoform. We also found that DC-SIGN is expressed by luminal breast cancer intratumoral macrophages. Moreover, experiments performed using semen fucosylated clusterin and monocyte derived macrophages showed that the interaction of semen clusterin with DC-SIGN promoted a proangiogenic profile, characterized by a high production of VEGF, IL-8 and TNF-α. Our results reveal an unexpected complexity on the structure and function of secretory clusterin produced by tumors and suggest that fucosylated clusterin produced by luminal breast cancer cells might play a role in tumor progression by promoting the release of pro-angiogenic factors by intratumoral macrophages.

Coillard A1,2, Segura E1. (2019 Aug 13)
In vivo Differentiation of Human Monocytes.
Frontiers in immunology : 10 : 1907 : DOI : 10.3389/fimmu.2019.01907

Résumé

Circulating monocytes can infiltrate mucosal or inflamed tissues where they differentiate into either macrophages or dendritic cells. This paradigm is supported by numerous studies conducted in mice and in different *in vitro* settings for human cells. Determining whether it holds true *in vivo* in humans is essential for the successful design of monocyte-targeting therapies. Despite limitations inherent to working with human samples, there is accumulating evidence of the existence of *in vivo*-generated monocyte-derived cells in humans. Here, we review recent studies showing the recruitment of human monocytes into tissues and their differentiation into macrophages or dendritic cells, in normal or pathological settings. We examine the methods available in human studies to demonstrate the monocytic origin of infiltrating cells. Finally, we review the functions of human monocyte-derived cells and how they might contribute to pathogeny.

Année de publication : 2015

Bonsang-Kitzis H1, Sadacca B2, Hamy-Petit AS3, Moarii M4, Pinheiro A3, Laurent C3, Reyal F1. (2019 Jun 24)
Biological network-driven gene selection identifies a stromal immune module as a key determinant of triple-negative breast carcinoma prognosis.
Oncoimmunology : 5 : 1061176 : DOI : 10.1080/2162402X.2015.1061176

Résumé

Triple-negative breast cancer (TNBC) is a heterogeneous group of aggressive breast cancers for which no targeted treatment is available. Robust tools for TNBC classification are required, to improve the prediction of prognosis and to develop novel therapeutic interventions. We analyzed 3,247 primary human breast cancer samples from 21 publicly available datasets, using a five-step method: (1) selection of TNBC samples by bimodal filtering on ER-HER2 and PR, (2) normalization of the selected TNBC samples, (3) selection of

the most variant genes, (4) identification of gene clusters and biological gene selection within gene clusters on the basis of String© database connections and gene-expression correlations, (5) summarization of each gene cluster in a metagene. We then assessed the ability of these metagenes to predict prognosis, on an external public dataset (METABRIC). Our analysis of gene expression (GE) in 557 TNBCs from 21 public datasets identified a six-metagene signature (167 genes) in which the metagenes were enriched in different gene ontologies. The gene clusters were named as follows: Immunity1, Immunity2, Proliferation/DNA damage, AR-like, Matrix/Invasion1 and Matrix2 clusters respectively. This signature was particularly robust for the identification of TNBC subtypes across many datasets (n = 1,125 samples), despite technology differences (Affymetrix© A, Plus2 and Illumina©). Weak Immunity two metagene expression was associated with a poor prognosis (disease-specific survival; HR = 2.68 [1.59-4.52], p = 0.0002). The six-metagene signature (167 genes) was validated over 1,125 TNBC samples. The Immunity two metagene had strong prognostic value. These findings open up interesting possibilities for the development of new therapeutic interventions.

Année de publication : 2019

Mélanie Durand, Thomas Walter, Tiphène Pirnay, Thomas Naessens, Paul Gueguen, Christel Goudot, Sonia Lameiras, Qing Chang, Nafiseh Talaei, Olga Ornatsky, Tatiana Vassilevskaia, Sylvain Baulande, Sebastian Amigorena, Elodie Segura (2019 May 11)

Human lymphoid organ cDC2 and macrophages play complementary roles in T follicular helper responses.

The Journal of experimental medicine : DOI : jem.20181994

Résumé

CD4 T follicular helper (Tfh) cells are essential for inducing efficient humoral responses. T helper polarization is classically orientated by dendritic cells (DCs), which are composed of several subpopulations with distinct functions. Whether human DC subsets display functional specialization for Tfh polarization remains unclear. Here we find that tonsil cDC2 and CD14 macrophages are the best inducers of Tfh polarization. This ability is intrinsic to the cDC2 lineage but tissue dependent for macrophages. We further show that human Tfh cells comprise two effector states producing either IL-21 or CXCL13. Distinct mechanisms drive the production of Tfh effector molecules, involving IL-12p70 for IL-21 and activin A and TGFβ for CXCL13. Finally, using imaging mass cytometry, we find that tonsil CD14 macrophages localize in situ in the B cell follicles, where they can interact with Tfh cells. Our results indicate that human lymphoid organ cDC2 and macrophages play complementary roles in the induction of Tfh responses.