Year of publication 2020

Pierre Bourdely, Giorgio Anselmi, Kristine Vaivode, Rodrigo Nalio Ramos, Yoann Missolo-Koussou, Sofia Hidalgo, Jimena Tosselo, Nicolas Nuñez, Wilfrid Richer, Anne Vincent-Salomon, Alka Saxena, Kristie Wood, Alvaro Lladser, Eliane Piaggio, Julie Helft, Pierre Guermonprez (2020 Jul 2)

Transcriptional and Functional Analysis of CD1c Human Dendritic Cells Identifies a CD163 Subset Priming CD8CD103 T Cells.

Immunity : 335-352.e8 : DOI : S1074-7613(20)30232-6

Summary

Dendritic cells (DCs) are antigen-presenting cells controlling T cell activation. In humans, the diversity, ontogeny, and functional capabilities of DC subsets are not fully understood. Here, we identified circulating CD88CD1cCD163 DCs (called DC3s) as immediate precursors of inflammatory CD88CD14CD1cCD163FcεRI DCs. DC3s develop via a specific pathway activated by GM-CSF, independent of cDC-restricted (CDP) and monocyte-restricted (cMoP) progenitors. Like classical DCs but unlike monocytes, DC3s drove activation of naive T cells. In vitro, DC3s displayed a distinctive ability to prime CD8 T cells expressing a tissue homing signature and the epithelial homing alpha-E integrin (CD103) through transforming growth factor β (TGF-β) signaling. In vivo, DC3s infiltrated luminal breast cancer primary tumors, and DC3 infiltration correlated positively with CD8CD103CD69 tissue-resident memory T cells. Together, these findings define DC3s as a lineage of inflammatory DCs endowed with a strong potential to regulate tumor immunity.

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

Summary

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.

Laetitia Boucault, Maria-Dolores Lopez Robles, Allan Thiolat, Séverine Bézie, Michael Schmueck-Henneresse, Cécile Braudeau, Nadège Vimond, Antoine Freuchet, Elodie Autrusseau, Frédéric Charlotte, Rabah Redjoul, Florence Beckerich, Mathieu Leclerc, Eliane Piaggio, Regis Josien, Hans-Dieter Volk, Sébastien Maury, José L Cohen, Ignacio Anegon, Carole Guillonneau (2020 Jun 9)

Transient antibody targeting of CD45RC inhibits the development of graft-versus-host disease.

Blood advances : 2501-2515 : DOI : 10.1182/bloodadvances.2020001688

Summary

Allogeneic bone marrow transplantation (BMT) is a widely spread treatment of many hematological diseases, but its most important side effect is graft-versus-host disease (GVHD). Despite the development of new therapies, acute GVHD (aGVHD) occurs in 30% to 50% of allogeneic BMT and is characterized by the generation of effector T (Teff) cells with production of inflammatory cytokines. We previously demonstrated that a short anti-CD45RC monoclonal antibody (mAb) treatment in a heart allograft rat model transiently decreased CD45RChigh Teff cells and increased regulatory T cell (Treg) number and function allowing long-term donor-specific tolerance. Here, we demonstrated in rat and mouse allogeneic GVHD, as well as in xenogeneic GVHD mediated by human T cells in NSG mice, that both ex vivo depletion of CD45RChigh T cells and in vivo treatment with short-course anti-CD45RC mAbs inhibited aGVHD. In the rat model, we demonstrated that long surviving animals treated with anti-CD45RC mAbs were fully engrafted with donor cells and developed a donor-specific tolerance. Finally, we validated the rejection of a human tumor in NSG mice infused with human cells and treated with anti-CD45RC mAbs. The anti-human CD45RC mAbs showed a favorable safety profile because it did not abolish human memory antiviral immune responses, nor trigger cytokine release in in vitro assays. Altogether, our results show the potential of a prophylactic treatment with anti-human CD45RC mAbs in combination with rapamycin as a new therapy to treat aGVHD without abolishing the antitumor effect.

Rodrigo Nalio Ramos, Céline Rodriguez, Margaux Hubert, Maude Ardin, Isabelle Treilleux, Carola H Ries, Emilie Lavergne, Sylvie Chabaud, Amélie Colombe, Olivier Trédan, Henrique Gomes Guedes, Fábio Laginha, Wilfrid Richer, Eliane Piaggio, José Alexandre M Barbuto, Christophe Caux, Christine Ménétrier-Caux, Nathalie Bendriss-Vermare (2020 Feb 22)

CD163 tumor-associated macrophage accumulation in breast cancer patients reflects both local differentiation signals and systemic skewing of monocytes.

Clinical & translational immunology : e1108 : DOI : 10.1002/cti2.1108

Summary

The accumulation of tumor-associated macrophages (TAMs) is correlated with poor clinical outcome, but the mechanisms governing their differentiation from circulating monocytes remain unclear in humans.

Mara De Martino, Mercedes Tkach, Sofía Bruni, Darío Rocha, María F Mercogliano, Mauro E Cenciarini, María F Chervo, Cecilia J Proietti, Florent Dingli, Damarys Loew, Elmer A Fernández, Patricia V Elizalde, Eliane Piaggio, Roxana Schillaci (2020 Feb 18)
Blockade of Stat3 oncogene addiction induces cellular senescence and reveals a cell-nonautonomous activity suitable for cancer immunotherapy.
Oncoimmunology : 1715767 : DOI : 10.1080/2162402X.2020.1715767

Summary

Stat3 is constitutively activated in several tumor types and plays an essential role in maintaining their malignant phenotype and immunosupression. To take advantage of the promising antitumor activity of Stat3 targeting, it is vital to understand the mechanism by which Stat3 regulates both cell autonomous and non-autonomous processes. Here, we demonstrated that turning off Stat3 constitutive activation in different cancer cell types induces senescence, thus revealing their Stat3 addiction. Taking advantage of the senescence-associated secretory phenotype (SASP) induced by Stat3 silencing (SASP-siStat3), we designed an immunotherapy. The administration of SASP-siStat3 immunotherapy induced a strong inhibition of triple-negative breast cancer and melanoma growth associated with activation of CD4 + T and NK cells. Combining this immunotherapy with anti-PD-1 antibody resulted in survival improvement in mice bearing melanoma. The characterization of the SASP components revealed that type I IFN-related mediators, triggered by the activation of the cyclic GMP-AMP synthase DNA sensing pathway, are important for its immunosurveillance activity. Overall, our findings provided evidence that administration of SASP-siStat3 or low dose of Stat3-blocking agents would benefit patients with Stat3-addicted tumors to unleash an antitumor immune response and to improve the effectiveness of immune checkpoint inhibitors.

Geoffrey M Lynn, Christine Sedlik, Faezzah Baharom, Yaling Zhu, Ramiro A Ramirez-Valdez, Vincent L Coble, Kennedy Tobin, Sarah R Nichols, Yaakov Itzkowitz, Neeha Zaidi, Joshua M Gammon, Nicolas J Blobel, Jordan Denizeau, Philippe de la Rochere, Brian J Francica, Brennan Decker, Mateusz Maciejewski, Justin Cheung, Hidehiro Yamane, Margery G Smelkinson, Joseph R Francica, Richard Laga, Joshua D Bernstock, Leonard W Seymour, Charles G Drake, Christopher M Jewell, Olivier Lantz, Eliane Piaggio, Andrew S Ishizuka, Robert A Seder (2020 Jan 15)
Peptide-TLR-7/8a conjugate vaccines chemically programmed for nanoparticle self-assembly enhance CD8 T-cell immunity to tumor antigens.
Nature biotechnology : 320-332 : DOI : 10.1038/s41587-019-0390-x

Summary

Personalized cancer vaccines targeting patient-specific neoantigens are a promising cancer treatment modality; however, neoantigen physicochemical variability can present challenges to manufacturing personalized cancer vaccines in an optimal format for inducing anticancer T cells. Here, we developed a vaccine platform (SNP-7/8a) based on charge-modified peptide-TLR-7/8a conjugates that are chemically programmed to self-assemble into nanoparticles of uniform size (~20 nm) irrespective of the peptide antigen composition. This approach provided precise loading of diverse peptide neoantigens linked to TLR-7/8a (adjuvant) in nanoparticles, which increased uptake by and activation of antigen-presenting cells that promote T-cell immunity. Vaccination of mice with SNP-7/8a using predicted neoantigens (n = 179) from three tumor models induced CD8 T cells against ~50% of neoantigens with high predicted MHC-I binding affinity and led to enhanced tumor clearance. SNP-7/8a delivering in silico-designed mock neoantigens also induced CD8 T cells in nonhuman primates. Altogether, SNP-7/8a is a generalizable approach for codelivering peptide antigens and adjuvants in nanoparticles for inducing anticancer T-cell immunity.

Year of publication 2019

Séverine Ménoret, Laure-Hélène Ouisse, Laurent Tesson, Séverine Remy, Claire Usal, Aude Guiffes, Vanessa Chenouard, Pierre-Joseph Royer, Gwenaelle Evanno, Bernard Vanhove, Eliane Piaggio, Ignacio Anegon (2019 Nov 26)
In Vivo Analysis of Human Immune Responses in Immunodeficient Rats.
Transplantation : 715-723 : DOI : 10.1097/TP.0000000000003047

Summary

Humanized immune system immunodeficient mice have been extremely useful for the in vivo analyses of immune responses in a variety of models, including organ transplantation and graft versus host disease (GVHD) but they have limitations. Rat models are interesting complementary alternatives presenting advantages over mice, such as their size and their active complement compartment. Immunodeficient rats have been generated but human immune responses have not yet been described.

Amaury Leruste, Jimena Tosello, Rodrigo Nalio Ramos, Arnault Tauzède-Espariat, Solène Brohard, Zhi-Yan Han, Kevin Beccaria, Mamy Andrianteranagna, Pamela Caudana, Jovan Nikolic, Céline Chauvin, Leticia Laura Niborski, Valeria Manriquez, Wilfrid Richer, Julien Masliah-Planchon, Sandrine Grossetête-Lalami, Mylene Bohec, Sonia Lameiras, Sylvain Baulande, Celio Pouponnot, Aurore Coulomb, Louise Galmiche, Didier Surdez, Nicolas Servant, Julie Helft, Christine Sedlik, Stéphanie Puget, Philippe Benaroch, Olivier Delattre, Joshua J Waterfall, Eliane Piaggio, Franck Bourdeaut (2019 Nov 12)
Clonally Expanded T Cells Reveal Immunogenicity of Rhabdoid Tumors.

Cancer cell : 597-612.e8 : DOI : S1535-6108(19)30482-9

Summary

Rhabdoid tumors (RTs) are genomically simple pediatric cancers driven by the biallelic inactivation of SMARCB1, leading to SWI/SNF chromatin remodeler complex deficiency. Comprehensive evaluation of the immune infiltrates of human and mice RTs, including immunohistochemistry, bulk RNA sequencing and DNA methylation profiling studies showed a high rate of tumors infiltrated by T and myeloid cells. Single-cell RNA (scRNA) and T cell receptor sequencing highlighted the heterogeneity of these cells and revealed therapeutically targetable exhausted effector and clonally expanded tissue resident memory CD8 T subpopulations, likely representing tumor-specific cells. Checkpoint blockade therapy in an experimental RT model induced the regression of established tumors and durable immune responses. Finally, we show that one mechanism mediating RTs immunogenicity involves SMARCB1-dependent re-expression of endogenous retroviruses and interferon-signaling activation.

Lecerf C, Kamal M, Vacher S, Chemlali W, Schnitzler A, Morel C, Dubot C, Jeannot E, Meseure D, Klijanienko J, Mariani O, Borcoman E, Calugaru V, Badois N, Chilles A, Lesnik M, Krhili S, Choussy O, Hoffmann C, Piaggio E, Bieche I, Le Tourneau C. (2019 Nov 3)
Immune gene expression in head and neck squamous cell carcinoma patients.
European journal of cancer : 121 : 210-223 : DOI : 10.1016/j.ejca

Summary

Jonathan G Pol, Pamela Caudana, Juliette Paillet, Eliane Piaggio, Guido Kroemer (2019 Oct 16)
Effects of interleukin-2 in immunostimulation and immunosuppression.
The Journal of experimental medicine : DOI : e20191247

Summary

Historically, interleukin-2 (IL-2) was first described as an immunostimulatory factor that supports the expansion of activated effector T cells. A layer of sophistication arose when regulatory CD4+ T lymphocytes (Tregs) were shown to require IL-2 for their development, homeostasis, and immunosuppressive functions. Fundamental distinctions in the nature and spatiotemporal expression patterns of IL-2 receptor subunits on naive/memory/effector T cells versus Tregs are now being exploited to manipulate the immunomodulatory effects of IL-2 for therapeutic purposes. Although high-dose IL-2 administration has yielded discrete clinical responses, low-dose IL-2 as well as innovative strategies based on IL-2 derivatives, including “muteins,” immunocomplexes, and immunocytokines, are being explored to therapeutically enhance or inhibit the immune response.

Aude Burlion, Rodrigo N Ramos, Pukar Kc, Kélhia Sendeyo, Aurélien Corneau, Christine Ménétrier-Caux, Eliane Piaggio, Daniel Olive, Christophe Caux, Gilles Marodon (2019 May 31)

A novel combination of chemotherapy and immunotherapy controls tumor growth in mice with a human immune system.

Oncoimmunology : 1596005 : DOI : 10.1080/2162402X.2019.1596005

Summary

Mice reconstituted with a human immune system and bearing human tumors represent a promising model for developing novel cancer immunotherapies. Here, we used mass cytometry and multi-parametric flow cytometry to characterize human leukocytes infiltrating a human breast cancer tumor model in immunocompromised NOD.SCID.γc-null mice reconstituted with a human immune system and compared it to samples of breast cancer patients. We observed highly activated human CD4 and CD8 T cells in the tumor, as well as minor subsets of innate immune cells in both settings. We also report that ICOS CD4 regulatory T cells (Treg) were enriched in the tumor relative to the periphery in humanized mice and patients, providing a target to affect Treg and tumor growth. Indeed, administration of a neutralizing mAb to human ICOS reduced Treg proportions and numbers and improved CD4 + T cell proliferation in humanized mice. Moreover, a combination of the anti-ICOS mAb with cyclophosphamide reduced tumor growth, and that was associated with an improved CD8 to Treg ratio. Depletion of human CD8 T cells or of murine myeloid cells marginally affected the effect of the combination therapy. Altogether, our results indicate that a combination of anti-ICOS mAb and chemotherapy controls tumor growth in humanized mice, opening new perspectives for the treatment of breast cancer. One sentence summary: Targeting ICOS in combination with chemotherapy is a promising strategy to improve tumor immunity in humans.

Edith Borcoman, Philippe De La Rochere, Wilfrid Richer, Sophie Vacher, Walid Chemlali, Clémentine Krucker, Nanour Sirab, Francois Radvanyi, Yves Allory, Géraldine Pignot, Nicolas Barry de Longchamps, Diane Damotte, Didier Meseure, Christine Sedlik, Ivan Bieche, Eliane Piaggio (2019 May 10)

Inhibition of PI3K pathway increases immune infiltrate in muscle-invasive bladder cancer.

Oncoimmunology : e1581556 : DOI : 10.1080/2162402X.2019.1581556

Summary

Although immune checkpoint inhibitors have shown improvement in survival in comparison to chemotherapy in urothelial bladder cancer, many patients still fail to respond to these treatments and actual efforts are made to identify predictive factors of response to immunotherapy. Understanding the tumor-intrinsic molecular basis, like oncogenic pathways conditioning the presence or absence of tumor-infiltrating T cells (TILs), should provide a new rationale for improved anti-tumor immune therapies. In this study, we found that urothelial bladder cancer from human samples bearing gene mutations was significantly associated with lower expression of a defined immune gene signature, compared to unmutated ones.

We identified a reduced 10-gene immune gene signature that discriminates muscle-invasive bladder cancer (MIBC) samples according to immune infiltration and mutation. Using a humanized mouse model, we observed that BKM120, a pan-PI3K inhibitor, significantly inhibited the growth of a human bladder cancer cell line bearing a mutation, associated to increased immune cell infiltration (hCD45+). Using qRT-PCR, we also found an increase in the expression of chemokines and immune genes in mutated tumors from mice treated with BKM120, reflecting an active immune infiltrate in comparison to untreated ones. Moreover, the addition of BKM120 rendered -mutated tumors sensitive to PD-1 blockade. Our results provide a relevant rationale for combination strategies of PI3K inhibitors with immune checkpoint inhibitors to overcome resistance to immune checkpoint inhibitors.

Pierre Guermonprez, Julie Helft (2019 Mar 13)
Inflammasome activation: a monocyte lineage privilege.
Nature immunology : 383-385 : DOI : 10.1038/s41590-019-0348-7

Summary

Pamela Caudana, Nicolas Gonzalo Núñez, Philippe De La Rochere, Anaïs Pinto, Jordan Denizeau, Ruby Alonso, Leticia Laura Niborski, Olivier Lantz, Christine Sedlik, Eliane Piaggio (2019 Jan 18)
IL2/Anti-IL2 Complex Combined with CTLA-4, But Not PD-1, Blockade Rescues Antitumor NK Cell Function by Regulatory T-cell Modulation.
Cancer immunology research : 443-457 : DOI : 10.1158/2326-6066.CIR-18-0697

Summary

High-dose IL2 immunotherapy can induce long-lasting cancer regression but is toxic and insufficiently efficacious. Improvements are obtained with IL2/anti-IL2 complexes (IL2Cx), which redirect IL2 action to CD8 T and natural killer (NK) cells. Here, we evaluated the efficacy of combining IL2Cx with blockade of inhibitory immune pathways. In an autochthonous lung adenocarcinoma model, we show that the IL2Cx/anti-PD-1 combination increases CD8 T-cell infiltration of the lung and controls tumor growth. In the B16-OVA model, which is resistant to checkpoint inhibition, combination of IL2Cx with PD-1 or CTLA-4 pathway blockade reverses that resistance. Both combinations work by reinvigorating exhausted intratumoral CD8 T cells and by increasing the breadth of tumor-specific T-cell responses. However, only the IL2Cx/anti-CTLA-4 combination is able to rescue NK cell antitumor function by modulating intratumoral regulatory T cells. Overall, association of IL2Cx with PD-1 or CTLA-4 pathway blockade acts by different cellular mechanisms, paving the way for the rational design of combinatorial antitumor therapies.

Year of publication 2018

Alexandra Frazao, Meriem Messaoudene, Nicolas Nunez, Nicolas Dulphy, France Roussin, Christine Sedlik, Laurence Zitvogel, Eliane Piaggio, Antoine Toubert, Anne Caignard (2018 Dec 6)

CD16NKG2A Natural Killer Cells Infiltrate Breast Cancer-Draining Lymph Nodes.
Cancer immunology research : 208-218 : DOI : 10.1158/2326-6066.CIR-18-0085

Summary

Tumor-draining lymph nodes (TD-LNs) are the first site of metastasis of breast cancer. Natural killer (NK) cells that infiltrate TD-LNs [including noninvaded (NI) or metastatic (M)-LNs from breast cancer patients] and NK cells from healthy donor (HD)-LNs were characterized, and their phenotype analyzed by flow cytometry. Low percentages of tumor cells invaded M-LNs, and these cells expressed ULBP2 and HLA class I molecules. Although NK cells from paired NI and M-LNs were similar, they expressed different markers compared with HD-LN NK cells. Compared with HD-LNs, TD-LN NK cells expressed activating DNAM-1, NKG2C and inhibitory NKG2A receptors, and exhibited elevated CXCR3 expression. CD16, NKG2A, and NKp46 expression were shown to be increased in stage IIIA breast cancer patients. TD-LNs contained a large proportion of activated CD56CD16 NK cells with high expression of NKG2A. We also showed that a subset of LN NK cells expressed PD-1, expression of which was correlated with NKp30 and NKG2C expression. LN NK cell activation status was evaluated by degranulation potential and lytic capacity toward breast cancer cells. NK cells from TD-LNs degranulated after coculture with breast cancer cell lines. Cytokine-activated TD-LN NK cells exerted greater lysis of breast cancer cell lines than HD-LN NK cells and preferentially lysed the HLA class I MCF-7 breast cancer cell line. TD-LNs from breast cancer patients, thus, contained activated lytic NK cells. The expression of inhibitory receptor NKG2A and checkpoint PD-1 by NK cells infiltrating breast cancer-draining LNs supports their potential as targets for immunotherapies using anti-NKG2A and/or anti-PD-1.