Année de publication : 2019

Hélène Salmon, Romain Remark, Sacha Gnjatic, Miriam Merad (2019 Mar 15)

Host tissue determinants of tumour immunity.

Nature Reviews Cancer : 215-227 : DOI : 10.1038/s41568-019-0125-9

Résumé

Although common evolutionary principles drive the growth of cancer cells regardless of the tissue of origin, the microenvironment in which tumours arise substantially differs across various organ sites. Recent studies have established that, in addition to cell-intrinsic effects, tumour growth regulation also depends on local cues driven by tissue environmental factors. In this Review, we discuss how tissue-specific determinants might influence tumour development and argue that unravelling the tissue-specific contribution to tumour immunity should help the development of precise immunotherapeutic strategies for patients with cancer.

Année de publication : 2018

Li Wang, Abdel Saci, Peter M Szabo, Scott D Chasalow, Mireia Castillo-Martin, Josep Domingo-Domenech, Arlene Siefker-Radtke, Padmanee Sharma, John P Sfakianos, Yixuan Gong, Ana Dominguez-Andres, William K Oh, David Mulholland, Alex Azrilevich, Liangyuan Hu, Carlos Cordon-Cardo, Hélène Salmon, Nina Bhardwaj, Jun Zhu, Matthew D Galsky (2018 Aug 31)

EMT- and stroma-related gene expression and resistance to PD-1 blockade in urothelial cancer.

Nature communications : 3503 : DOI : 10.1038/s41467-018-05992-x

Résumé

Cancers infiltrated with T-cells are associated with a higher likelihood of response to PD-1/PD-L1 blockade. Counterintuitively, a correlation between epithelial-mesenchymal transition (EMT)-related gene expression and T-cell infiltration has been observed across tumor types. Here we demonstrate, using The Cancer Genome Atlas (TCGA) urothelial cancer dataset, that although a gene expression-based measure of infiltrating T-cell abundance and EMT-related gene expression are positively correlated, these signatures convey disparate prognostic information. We further demonstrate that non-hematopoietic stromal cells are a major source of EMT-related gene expression in bulk urothelial cancer transcriptomes. Finally, using a cohort of patients with metastatic urothelial cancer treated with a PD-1 inhibitor, nivolumab, we demonstrate that in patients with T-cell infiltrated tumors, higher EMT/stroma-related gene expression is associated with lower response rates and shorter progression-free and overall survival. Together, our findings suggest a stroma-mediated source of immune resistance in urothelial cancer and provide rationale for co-targeting PD-1 and stromal elements.

Margaret E Kirkling, Urszula Cytlak, Colleen M Lau, Kanako L Lewis, Anastasia Resteu, Alireza Khodadadi-Jamayran, Christian W Siebel, Hélène Salmon, Miriam Merad, Aristotelis Tsirigos, Matthew Collin, Venetia Bigley, Boris Reizis (2018 Jun 21)

Notch Signaling Facilitates In Vitro Generation of Cross-Presenting Classical Dendritic Cells.

Cell reports : 3658-3672.e6 : DOI : S2211-1247(18)30832-5

Résumé

The IRF8-dependent subset of classical dendritic cells (cDCs), termed cDC1, is important for cross-priming cytotoxic T cell responses against pathogens and tumors. Culture of hematopoietic progenitors with DC growth factor FLT3 ligand (FLT3L) yields very few cDC1s (in humans) or only immature « cDC1-like » cells (in the mouse). We report that OP9 stromal cells expressing the Notch ligand Delta-like 1 (OP9-DL1) optimize FLT3L-driven development of cDC1s from murine immortalized progenitors and primary bone marrow cells. Co-culture with OP9-DL1 induced IRF8-dependent cDC1s with a phenotype (CD103 Dec205 CD8α) and expression profile resembling primary splenic cDC1s. OP9-DL1-induced cDC1s showed preferential migration toward CCR7 ligands in vitro and superior T cell cross-priming and antitumor vaccination in vivo. Co-culture with OP9-DL1 also greatly increased the yield of IRF8-dependent CD141 cDC1s from human bone marrow progenitors cultured with FLT3L. Thus, Notch signaling optimizes cDC generation in vitro and yields authentic cDC1s for functional studies and translational applications.

Année de publication : 2017

Brandon Hogstad, Marie-Luise Berres, Rikhia Chakraborty, Jun Tang, Camille Bigenwald, Madhavika Serasinghe, Karen Phaik Har Lim, Howard Lin, Tsz-Kwong Man, Romain Remark, Samantha Baxter, Veronika Kana, Stefan Jordan, Zoi Karoulia, Wing-Hong Kwan, Marylene Leboeuf, Elisa Brandt, Helene Salmon, Kenneth McClain, Poulikos Poulikakos, Jerry Chipuk, Willem J M Mulder, Carl E Allen, Miriam Merad (2017 Dec 22)

RAF/MEK/extracellular signal-related kinase pathway suppresses dendritic cell migration and traps dendritic cells in Langerhans cell histiocytosis lesions.

The Journal of experimental medicine : 319-336 : DOI : 10.1084/jem.20161881

Résumé

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by granulomatous lesions containing pathological CD207 dendritic cells (DCs) with constitutively activated mitogen-activated protein kinase (MAPK) pathway signaling. Approximately 60% of LCH patients harbor somatic V600E mutations localizing to CD207 DCs within lesions. However, the mechanisms driving V600E LCH cell accumulation in lesions remain unknown. Here we show that sustained extracellular signal-related kinase activity induced by V600E inhibits C-C motif chemokine receptor 7 (CCR7)-mediated DC migration, trapping DCs in tissue lesions. Additionally, V600E increases expression of BCL2-like protein 1 (BCL2L1) in

DCs, resulting in resistance to apoptosis. Pharmacological MAPK inhibition restores migration and apoptosis potential in a mouse LCH model, as well as in primary human LCH cells. We also demonstrate that MEK inhibitor-loaded nanoparticles have the capacity to concentrate drug delivery to phagocytic cells, significantly reducing off-target toxicity. Collectively, our results indicate that MAPK tightly suppresses DC migration and augments DC survival, rendering DCs in LCH lesions trapped and resistant to cell death.

Année de publication : 2016

Hélène Salmon, Juliana Idoyaga, Adeeb Rahman, Marylène Leboeuf, Romain Remark, Stefan Jordan, Maria Casanova-Acebes, Makhzuna Khudoynazarova, Judith Agudo, Navpreet Tung, Svetoslav Chakarov, Christina Rivera, Brandon Hogstad, Marcus Bosenberg, Daigo Hashimoto, Sacha Gnjatic, Nina Bhardwaj, Anna Karolina Palucka, Brian D Brown, Joshua Brody, Florent Ginhoux, Miriam Merad (2016 Apr 21)

Expansion and Activation of CD103(+) Dendritic Cell Progenitors at the Tumor Site Enhances Tumor Responses to Therapeutic PD-L1 and BRAF Inhibition.

Immunity : 924-38 : DOI : 10.1016/j.immuni.2016.03.012

Résumé

Large numbers of melanoma lesions develop resistance to targeted inhibition of mutant BRAF or fail to respond to checkpoint blockade. We explored whether modulation of intratumoral antigen-presenting cells (APCs) could increase responses to these therapies. Using mouse melanoma models, we found that CD103(+) dendritic cells (DCs) were the only APCs transporting intact antigens to the lymph nodes and priming tumor-specific CD8(+) T cells. CD103(+) DCs were required to promote anti-tumoral effects upon blockade of the checkpoint ligand PD-L1; however, PD-L1 inhibition only led to partial responses. Systemic administration of the growth factor FLT3L followed by intratumoral poly I:C injections expanded and activated CD103(+) DC progenitors in the tumor, enhancing responses to BRAF and PD-L1 blockade and protecting mice from tumor rechallenge. Thus, the paucity of activated CD103(+) DCs in tumors limits checkpoint-blockade efficacy and combined FLT3L and poly I:C therapy can enhance tumor responses to checkpoint and BRAF blockade.

Année de publication : 2015

Jeremy G Price, Juliana Idoyaga, Hélène Salmon, Brandon Hogstad, Carolina L Bigarella, Saghi Ghaffari, Marylene Leboeuf, Miriam Merad (2015 Sep 8)

CDKN1A regulates Langerhans cell survival and promotes Treg cell generation upon exposure to ionizing irradiation.

Nature immunology : 1060-8 : DOI : 10.1038/ni.3270

Résumé

Treatment with ionizing radiation (IR) can lead to the accumulation of tumor-infiltrating regulatory T cells (Treg cells) and subsequent resistance of tumors to radiotherapy. Here we focused on the contribution of the epidermal mononuclear phagocytes Langerhans cells (LCs) to this phenomenon because of their ability to resist depletion by high-dose IR. We found that LCs resisted apoptosis and rapidly repaired DNA damage after exposure to IR. In particular, we found that the cyclin-dependent kinase inhibitor CDKN1A (p21) was overexpressed in LCs and that Cdkn1a(-/-) LCs underwent apoptosis and accumulated DNA damage following IR treatment. Wild-type LCs upregulated major histocompatibility complex class II molecules, migrated to the draining lymph nodes and induced an increase in Treg cell numbers upon exposure to IR, but Cdkn1a(-/-) LCs did not. Our findings suggest a means for manipulating the resistance of LCs to IR to enhance the response of cutaneous tumors to radiotherapy.

Miriam Merad, Hélène Salmon (2015 Jul 17)
Cancer: A dendritic-cell brake on antitumour immunity.
Nature : 294-5 : DOI : 10.1038/523294a

Résumé

Année de publication : 2013

Judith Agudo, Albert Ruzo, Navpreet Tung, Hélène Salmon, Marylène Leboeuf, Daigo Hashimoto, Christian Becker, Lee-Ann Garrett-Sinha, Alessia Baccarini, Miriam Merad, Brian D Brown (2013 Nov 26)
The miR-126-VEGFR2 axis controls the innate response to pathogen-associated nucleic acids.
Nature immunology : 54-62 : DOI : 10.1038/ni.2767

Résumé

miR-126 is a microRNA expressed predominately by endothelial cells and controls angiogenesis. We found miR-126 was required for the innate response to pathogen-associated nucleic acids and that miR-126-deficient mice had greater susceptibility to infection with pseudotyped HIV. Profiling of miRNA indicated that miR-126 had high and specific expression by plasmacytoid dendritic cells (pDCs). Moreover, miR-126 controlled the survival and function of pDCs and regulated the expression of genes encoding molecules involved in the innate response, including Tlr7, Tlr9 and Nfkb1, as well as Kdr, which encodes the growth factor receptor VEGFR2. Deletion of Kdr in DCs resulted in reduced production of type I interferon, which supports the proposal of a role for VEGFR2 in miR-126 regulation of pDCs. Our studies identify the miR-126-VEGFR2 axis as an important regulator of the innate response that operates through multiscale control of pDCs.

Elisa Peranzoni, Ana Rivas-Caicedo, Houcine Bougherara, Hélène Salmon, Emmanuel Donnadieu

(2013 May 8)
Positive and negative influence of the matrix architecture on antitumor immune surveillance.
Cellular and molecular life sciences : CMLS : 4431-48 : DOI : 10.1007/s00018-013-1339-8

Résumé

The migration of T cells and access to tumor antigens is of utmost importance for the induction of protective anti-tumor immunity. Once having entered a malignant site, T cells encounter a complex environment composed of non-tumor cells along with the extracellular matrix (ECM). It is now well accepted that a deregulated ECM favors tumor progression and metastasis. Recent progress in imaging technologies has also highlighted the impact of the matrix architecture found in solid tumor on immune cells and especially T cells. In this review, we argue that the ability of T cells to mount an antitumor response is dependent on the matrix structure, more precisely on the balance between pro-migratory reticular fiber networks and unfavorable migration zones composed of dense and aligned ECM structures. Thus, the matrix architecture, that has long been considered to merely provide the structural framework of connective tissues, can play a key role in facilitating or suppressing the antitumor immune surveillance. A new challenge in cancer therapy will be to develop approaches aimed at altering the architecture of the tumor stroma, rendering it more permissive to antitumor T cells.

Année de publication : 2012

Hélène Salmon, Katarzyna Franciszkiewicz, Diane Damotte, Marie-Caroline Dieu-Nosjean, Pierre Validire, Alain Trautmann, Fathia Mami-Chouaib, Emmanuel Donnadieu (2012 Feb 2)
Matrix architecture defines the preferential localization and migration of T cells into the stroma of human lung tumors.
The Journal of clinical investigation : 899-910 : DOI : 10.1172/JCI45817

Résumé

Appropriate localization and migration of T cells is a prerequisite for antitumor immune surveillance. Studies using fixed tumor samples from human patients have shown that T cells accumulate more efficiently in the stroma than in tumor islets, but the mechanisms by which this occurs are unknown. By combining immunostaining and real-time imaging in viable slices of human lung tumors, we revealed that the density and the orientation of the stromal extracellular matrix likely play key roles in controlling the migration of T cells. Active T cell motility, dependent on chemokines but not on β1 or β2 integrins, was observed in loose fibronectin and collagen regions, whereas T cells migrated poorly in dense matrix areas. Aligned fibers in perivascular regions and around tumor epithelial cell regions dictated the migratory trajectory of T cells and restricted them from entering tumor islets. Consistently, matrix reduction with collagenase increased the ability of T cells to contact cancer cells. Thus, the stromal extracellular matrix influences antitumor immunity by controlling the positioning and migration of T cells. Understanding the mechanisms by which this collagen

network is generated has the potential to aid in the development of new therapeutics.

Année de publication : 2011

Hélène Salmon, Ana Rivas-Caicedo, François Asperti-Boursin, Camille Lebugle, Pierre Bourdoncle, Emmanuel Donnadieu (2011 Jul 22)

Ex vivo imaging of T cells in murine lymph node slices with widefield and confocal microscopes.

Journal of visualized experiments : JoVE : e3054 : DOI : 10.3791/3054

Résumé

Naïve T cells continuously traffic to secondary lymphoid organs, including peripheral lymph nodes, to detect rare expressed antigens. The migration of T cells into lymph nodes is a complex process which involves both cellular and chemical factors including chemokines. Recently, the use of two-photon microscopy has permitted to track T cells in intact lymph nodes and to derive some quantitative information on their behavior and their interactions with other cells. While there are obvious advantages to an in vivo system, this approach requires a complex and expensive instrumentation and provides limited access to the tissue. To analyze the behavior of T cells within murine lymph nodes, we have developed a slice assay, originally set up by neurobiologists and transposed recently to murine thymus. In this technique, fluorescently labeled T cells are plated on top of an acutely prepared lymph node slice. In this video-article, the localization and migration of T cells into the tissue are analyzed in real-time with a widefield and a confocal microscope. The technique which complements in vivo two-photon microscopy offers an effective approach to image T cells in their natural environment and to elucidate mechanisms underlying T cell migration.