LÍNEA DE INVESTIGACIÓN:

Molecular mechanisms of cancer immune escape: analysis and correction of MHC class I alterations

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Resumen línea de investigación

Recognition of tumor-associated antigens (TAA) by self-MHC (Major Histocompatibility Antigens or HLA in humans) class I-restricted CD8+ T cells is a main feature in the detection and destruction of malignant cells. Currently, tumor immunology and oncology has focused on targeting 'tumor escape phase' to increase tumor immunogenicity and on developing new therapeutic modalities. The discovery and molecular characterization of TAA has changed the field of cancer treatment and introduced a new era of cancer immunotherapy aimed at increasing tumor immunogenicity and T-cell-mediated anti-tumor immunity. Unfortunately, while these new protocols of cancer immunotherapy are mediating induction of tumor-specific T lymphocytes in patients with certain malignancies, they have not yet delivered substantial clinical benefits, such as induction of tumor regression or increased disease-free survival. It has become apparent that lack of tumor rejection is the result of immune selection and escape by tumor cells that develop low immunogenic phenotypes. Substantial experimental data support the existence of a variety of different mechanisms involved in the tumor escape phase, including loss or downregulation of MHC class I antigens. Malignant behavior of a tumor cell may depend on the level of MHC class I expression and alterations in tumor MHC class I antigens may be a factor in escape from immune surveillance. These alterations could be caused by reversible/regulatory changes or by structural/irreversible genetic defects, including mutations/deletions and chromosomal aberrations in genes coding for MHC molecules. Different mechanisms underlie these alterations and might require different therapeutic approach. On the basis of the evidence obtained from experimental mouse cancer models and metastatic human tumors, the structural defects underlying MHC class I loss may have more profound implications on T-cell-mediated tumor rejection and ultimately on the outcome of cancer immunotherapy. It may lead to resistance to immunomodulatory therapy and generation of dangerous MHC class I-negative tumor escape variants. Strategies to overcome this obstacle, including gene therapy to recover normal expression of MHC class I genes, could increase tumor immunogenicity and improve the efficacy of immunotherapeutic modalities.

Currently we are investigating:

- molecular mechanisms of HLA class I alterations during various phases of cancer immune escape;
- association of these alterations with the cancer progression, metastatic dissemination, reorganization of tumor microenvironment and resistance to cancer immunotherapy;
- correlation between the expression of tumor HLA class I and "immune checkpoint" molecules (PD-L1);
- gene therapy approach to recover normal HLA class I expression in tumor cells
- analysis of HLA-I and PD-L1 expression in liquid biopsy (tumor derived exosomes and cfDNA) for detection of HLA class I alterations in cancer patients.

RECENT PUBLICATIONS

1) Garrido F, **Aptsiauri N**. Cancer immune escape: MHC expression in primary tumours versus metastases. Immunology. 2019 Dec;158(4):255-266. doi: 10.1111/imm.13114.

2) Flores-Martín JF, Perea F, Exposito-Ruiz M, Carretero FJ, Rodriguez T, Villamediana M, Ruiz-Cabello F, Garrido F, Cózar-Olmo JM, **Aptsiauri N.** A Combination of Positive Tumor HLA-I and Negative PD-L1 Expression Provides an Immune Rejection Mechanism in Bladder Cancer. Ann Surg Oncol. 2019 Aug;26(8):2631-2639. doi: 10.1245/s10434-019-07371-2.

3) Garrido MA, Rodriguez T, Zinchenko S, Maleno I, Ruiz-Cabello F, Concha Á, Olea N, Garrido F, **Aptsiauri N.** HLA class I alterations in breast carcinoma are associated with a high frequency of the loss of heterozygosity at chromosomes 6 and 15.
Immunogenetics. 2018 Nov;70(10):647-659.

4) **Aptsiauri N**, Ruiz-Cabello F, Garrido F. The transition from HLA-I positive to HLA-I negative primary tumors: the road to escape from T-cell responses. Curr Opin Immunol. 2018 Apr;51:123-132.

5) Perea F, Sánchez-Palencia A, Gómez-Morales M, Bernal M, Concha Á, García MM, González-Ramírez AR, Kerick M, Martin J, Garrido F, Ruiz-Cabello F, **Aptsiauri N**. HLA class I loss and PD-L1 expression in lung cancer: impact on T-cell infiltration and immune escape. Oncotarget. 2017 Dec 19;9(3):4120-4133.

6) Garrido F, Perea F, Bernal M, Sánchez-Palencia A, **Aptsiauri N**, Ruiz-Cabello F. The Escape of Cancer from T Cell-Mediated Immune Surveillance: HLA Class I Loss and Tumor Tissue Architecture. Vaccines (Basel)., 2017 Feb 27;5(1), pii: E7.

7) Garrido F, Ruiz-Cabello F, **Aptsiauri N**. Rejection versus escape: the tumor MHC dilemma. Cancer Immunol Immunother. 2017 Feb;66(2):259-271.

8) **Aptsiauri N**, Jewett A, Hurwitz AA, Shurin MR, Umansky V. Redefining cancer immunotherapy-optimization, personalization, and new predictive biomarkers: 4th Cancer Immunotherapy and Immunomonitoring (CITIM) meeting, April 27-30, 2015, Ljubljana, Slovenia. Cancer Immunol Immunother. 2016 Jul;65(7):875-83

9) Carretero FJ, Del Campo A, Zinchenko S, Garrido F, **Aptsiauri N.** Recovery of HLA-A2 and Beta2-microglobulin Expression in Tumor Cells Using Viral Vectors. Journal of Cancer Science & Therapy, 2017, 9:9

10) Carretero FJ, Del Campo AB, Flores-Martín JF, Mendez R, García-Lopez C, Cozar JM, Adams V, Ward S, Cabrera T, Ruiz-Cabello F, Garrido F, **Aptsiauri N.** Frequent HLA class I alterations in human prostate cancer: molecular mechanisms and clinical relevance. Cancer Immunol Immunother. 2016 Jan;65(1):47-59.

11) Garrido F, **Aptsiauri N**, Doorduijn EM, Garcia Lora AM, van Hall T. The urgent need to recover MHC class I in cancers for effective immunotherapy. Curr Opin Immunol. 2016 Apr;39:44-51.

12) Garrido F, I.Romero, **Aptsiauri N**, A.Garcia-Lora. Generation of MHC class I diversity in primary tumors and selection of the malignant phenotype. International Journal of Cancer, 2016 Jan 15;138(2):271-80.

13) Del Campo AB, Carretero J, Muñoz JA, Zinchenko S, Ruiz-Cabello F, González-Aseguinolaza G, Garrido F, **Aptsiauri N.**
Adenovirus expressing β2-microglobulin recovers HLA class I expression and antitumor immunity by increasing T-cell recognition. Cancer Gene Therapy ,2014 Aug;21(8):317-32.

14) Ana B. Del Campo , Jon Amund Kyte, Javier Carretero, Svitlana Zinchencko , Rosa Méndez ,Gloria González-Aseguinolaza, Francisco Ruiz-Cabello1, Steinar Aamdal, Gustav Gaudernack , Federico Garrido , **Natalia Aptsiauri.** Immune escape of cancer cells with beta2-microglobulin loss over the course of metastatic melanoma. International Journal of Cancer ,2014 Jan 1;134(1):102-13.

15) **N. Aptsiauri**, AM. Garcia-Lora, F.Garrido. 'Hard' and 'soft' loss of MHC class I expression in cancer cells. Book chapter In: Tumor Immunology and Immunotherapy. Editor: Robert Rees, Oxford University Press. 2014, p 63-78

16) **Aptsiauri N,** Garcia-Lora A, Cabrera T. MHC Class I antigens in malignant cells: Immune escape and response to immunotherapy.
Book. Springer Briefs in Cancer Research, Springer (New York, Heidelberg, Dordrecht, London), 2013, 51 pages.

RESEARCH PROJECTS

Título: Incremento de la inmunogenicidad en células tumorales tras la restauración de la expresión de HLA de clase I mediante vectores adenovirales.
AGENCIA FINANCIADORA: Junta de Andalucía, Consejería de Salud, PI-0382
DURACION: 2009-2011
Investigador Principal - Natalia Aptsiauri

Título: HLA de clase I en la progresión metastásica y la resistencia a la inmunoterapia de nueva generación: Implicaciones en el escape inmunológico del cáncer
AGENCIA FINANCIADORA: AES 2014 Proyectos de investigación en salud, PI 14/01978
DURATION: 2014-2017
Co-Investigador Principal – N. Aptsiauri, IP-F. Garrido

Título: Transferencia de genes HLA a líneas celulares tumorales con alteraciones conocidas para la expresión HLA de clase I – la utilización de vectores adenovirales.
AGENCIA FINANCIADORA: Fondo de Investigaciones Sanitarias (FIS), Instituto de Salud Carlos III, FIS 04/00245
DURACION: 2005-2008
Investigador Principal: N. Aptsiauri

Título: Alteración de la presentación antigénica en las células tumorales: implicación en la inmunovigilancia e inmunoterapia.
AGENCIA FINANCIADORA: - Instituto de Salud Carlos III, PI17/00197
DURATION: 2018-2020
Colaboratora (IP-F.Garrido)

Título: Virus adeno-asociado en terapia génica del cáncer
AGENCIA FINANCIADORA: Servicio Andaluz de Salud (SAS), Conserjería de salud y bienestar social, estancia formativa, SAS EF-1093-2012
DURACIÓN: 2012
Investigador Principal: Natalia Aptsiauri

Título: Las moléculas HLA y el escape inmunológico del cáncer: estudios de metástasis que progresan y regresan en pacientes sometidos a inmunoterapia.
Entintad Financiadora: Proyecto de investigación de excelencia, Consejería de Salud, Junta de Andalucía, CTS-3952
DURACIÓN: 2009-2012
Colaboradora (IP – F.Garrido)

Título: El escape del cáncer a la inmunovigilancia: expresión de MHC y rechazo tumoral.
AGENCIA FINANCIADORA: Instituto de Salud Carlos III, PI11/01022
DURACIÓN: 2012-2014
Colaboradora, (IP – F.Garrido)

8) RED NACIONAL DE BIOBANCOS, Nº expediente: PT13/0010/0039
AGENCIA FINANCIADORA: Instituto de Salud Carlos III
DURACIÓN: 2013-2014
Colaboradora, (IP – F.Garrido)

Título: Restitución de la inmunogenicidad del cáncer mediante el uso de vectores adenovirales y genes HLA
AGENCIA FINANCIADORA: PROYECTOS DE EXCELENCIA, JUNTA DE ANDALUCÍA, CVI-4740
DURACIÓN: 2009-2013
Colaboradora, (IP – F.Garrido)

PhD Thesis

1) “Beta-2-microglobulin gene transfer in HLA class I deficient tumor cells using recombinant adenovirus” Doctorado Internacional, Universidad de Granada, 2014

2) “Analysis of the molecular mechanism of HLA altered expression in prostate cancer and its recuperation using viral vectors”, Doctorado Internacional, Universidad de Granada, 2016

MASTER THESIS

1) M. Mendez Garcia - “Estudio de la relación entre la expresión de HLA de tipo I y de distintos receptores “inmune checkpoints”. 2014-2015

2) M. Villamediana Abad - “Expresión de HLA-I, PD-L1 y caracterización del microambiente tumoral (PD-1, CD3, CD8, CXCR-4, FAP1 Y CD80) en cáncer de vejiga”, 2015-16

3) JR Hernández Caicedo - “Expresión de HLA de clase I y otras moléculas inmuno-reguladoras (PD-L1, CD80, CXCR4) en líneas tumorales derivadas de cáncer de colon primario y metástasis hepática antólogo”, 2015-2016.

4) JA López Sánchez – “Análisis de expresión de HLA de clase I en exosomas de líneas tumorales”, 2016-17

5) Berit Brinkman (Universidad de Essen, Alemania) – “Characterisation of Major Histocompatibility Complex I (MHC-I) phenotypes in tumour derived exosomesia) – 2016-17

6) N Blanco Gómez - “Expresión de los antígenos HLA de clase I Y II en cáncer colorrectal primario y metástasis”, 2016-17

7) A Navarro Ocón – “Análisis de la expresión del HLA-I en exosomas de pacientes de cáncer de pulmón” - 2017-2018

8) L Cabo Zabala – “Biopsia líquida: Análisis de la expresión de HLA-I en melanoma”, 2018-19

9) JM Andrés de la Cruz – “Interacción de las células tumorales con fibroblastos: implicaciones en la pérdida de HLA-I en el escape inmunológico y en la reorganización del microambiente tumoral” – 2019-20