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) A**ptsiauri N**, Garrido F The Challenges of HLA Class I Loss in Cancer Immunotherapy: Facts and Hopes. Clin Cancer Res. 2022 Dec 1;28(23):5021-5029. doi: 10.1158/1078-0432.CCR-21-3501.

2) Navarro-Ocón A, Blaya-Cánovas JL, López-Tejada A, Blancas I, Sánchez-Martín RM, Garrido MJ, Griñán-Lisón C, Calahorra J, Cara FE, Ruiz-Cabello F, Marchal JA, **Aptsiauri N**, Granados-Principal S. Nanomedicine as a Promising Tool to Overcome Immune Escape in Breast Cancer.
Pharmaceutics. 2022 Feb 25;14(3):505. doi: 10.3390/pharmaceutics14030505.

3) Garrido MA, Perea F, Vilchez JR, Rodríguez T, Anderson P, Garrido F, Ruiz-Cabello F, **Aptsiauri N**. Copy Neutral LOH Affecting the Entire Chromosome 6 Is a Frequent Mechanism of HLA Class I Alterations in Cancer. Cancers (Basel). 2021 Oct 9;13(20):5046. doi: 10.3390/cancers13205046.

4) Gil-Julio H, Perea F, Rodriguez-Nicolas A, Cozar JM, González-Ramirez AR, Concha A, Garrido F, **Aptsiauri N**, Ruiz-Cabello F. Tumor Escape Phenotype in Bladder Cancer Is Associated with Loss of HLA Class I Expression, T-Cell Exclusion and Stromal Changes. Int J Mol Sci. 2021 Jul 6;22(14):7248. doi: 10.3390/ijms22147248.

5) Anderson P, **Aptsiauri N**, Ruiz-Cabello F, Garrido F. HLA class I loss in colorectal cancer: implications for mmune escape and immunotherapy. Cell Mol Immunol. 2021 Mar;18(3):556-565. doi: 10.1038/s41423-021-00634-7

6) 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.

7) 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.

8) 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. doi: 10.1007/s00251-018-1074-2.

9) 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.

10) 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.

11) 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.

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

13) 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

14) 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

15) 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.

16) 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.

17) 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.

18) Del Campo AB, Carretero J, Muñoz JA, Zinchenko S, Ruiz-Cabello F, González-Aseguinolaza G, Garrido F, **Aptsiauri N.**

19) 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.

20) 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.

21) **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

22) **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.

RECENT RESEARCH PROJECTS

Título: Cancer immune escape and alterations in MHC genes: analysis of tumor derived extracellular vesicles and cfDNA
Entidad Financiadora: Agencia Estatal de Investigación. Ministerio de Ciencia e Innovación,
Codigo: PID2020-115087GB-100
Duracion: 2021 - 2024
Financiación obtenida: 118.000€
IP: Natalia Aptsiauri

Titulo: Detección de las Alteraciones en HLA de Clase I en Biopsia Líquida Como Biomarcador Tumoral de Resistencia a la Inmunoterapia
Referencia: B-CTS-410-UGR20
Proyectos de I+D+i en el marco del Programa Operativo FEDER
Duracion: 2021 - 2023
Financiación obtenida: 50.000€
Co-IP: Natalia Aptsiauri; IP: F. Ruiz-Cabello

Titulo: Modulación de la homeostasis de las células del estroma intestinal por el microbioma intestinal: impacto en la enfermedad inflamatoria intestinal y el cáncer colorrectal
Entidad Financiadora: FIS, Instituto de Salud Carlos III, PI22/01630
Duracion: 2022 - 01/09/2025
Financiación obtenida: 205.034,50 €
Colaboradora, IP - Maria Elena Rodriguez Cabezas

Titulo: STEM-ITRUCK: células CAR-T de última generación para el tratamiento seguro y eficaz de tumores sólidos
Entidad Financiadora: Consejería de Transformación Económica, Industria, Conocimiento y Universidades, Junta de Andalucia, Plan Andaluz de Investigación, Desarrollo e Innovación (PAIDI 2020)
Financiación obtenida:157.596,00€
Colaboradora, IP - Verónica Pilar Ayllón Cases

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
Financiación obtenida:150.000,00€
Colaboratora (IP-F.Garrido)

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-IP - N. Aptsiauri, 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

Currently supervising 3 doctoral thesis

MASTER THESIS

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

2) MVA - “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 HC - “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) JALS – “Análisis de expresión de HLA de clase I en exosomas de líneas tumorales”, 2016-17

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

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

7) ANavarro O – “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 A 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

10) VRD - "Análisis comparativo de HLA de clase I e immune checkpoints en líneas celulares de melanoma en el escape inmunológico y en la reorganización del microambiente tumoral” – 2019-20

11) JPC - “HLA in lineas de cáncer colorrectal derivadas de tumores primarios y metástasis autólogas” - 2019-20

12) RLA - "Análisis comparativo de la expresión de nuevos immune checkpoints” CD155 y CD112 en líneas celulares de melanoma humanas HLA-I positivas y negativas" - 2021-22

13) PMG - " Estudio comparativo entre cáncer renal y vejiga: papel de las moleculas HLA de clase I y CD70 en la progresión tumoral" - 2022-23

14) PCG - " Quimiorresistencia y alteraciones de HLA en leucemia:¿Relación algo más que circunstancial? - 2022-23