

Federico Garrido

# MHC Class-I Loss and Cancer Immune Escape

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Federico Garrido

MHC Class-I Loss  
and Cancer  
Immune Escape

 Springer

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The work presented in this book summarizes decades of research focused on analyzing the expression of histocompatibility antigens in mouse and human tumors (H-2 and HLA) in the Dept. of Analisis Clinicos e Inmunologia at Hospital Universitario “Virgen de las Nieves” in Granada, Spain. I would like to acknowledge all the members of the research team for their contributions. Most importantly, I would like to thank the cancer patients in our hospital and from different European clinical and research institutions who gave their consent to analyze their tumor samples. I would like to mention Dr. Matias Perez who started to work with me in 1979 and initiated the mouse work at the beginning of the 1980s by inducing experimental sarcomas with methylcholanthrene and typing different tumor clones for H-2 antigens. One of these tumors, the GR9, and all the different tumor clones obtained have been studied for more than 20 years by him and other researchers in our group, Ignacio Algarra, Jose Juan Gaforio, and Angel Garcia Lora. These studies have generated important discoveries. We have learned a lot and are still obtaining new data from the GR9 tumor model. Dr. Teresa Cabrera set up the immunohistological laboratory and developed tumor microdissection techniques to study HLA expression in human tumor tissues. She selected a large variety of monoclonal antibodies that recognize different HLA antigens in tumor tissues and participated in the International HLA workshop in France where the “HLA and cancer” component was introduced for the first time. Dr. Francisco Ruiz-Cabello applied different molecular and flow cytometry techniques to identify and characterize molecular mechanisms responsible for HLA alterations. He and his team, including Drs. Pilar Jimenez and Isabel Maleno, made important contributions to the field. Dr. Miguel Angel Lopez-Nevot in the early days focused on melanoma and on genomic HLA typing of tumors, helping to develop the immunofluorescence techniques with anti-HLA monoclonal antibodies. Dr. Natalia Aptsiauri brought her enormous international experience to our team, which she had gained from different USA labs, and collaborated with me in writing different reviews and taking strategic decisions in our work. All of them currently are holding important academic and research positions at the University of Granada and Jaen, as well as in the Tumour Tissue Biobank of the Hospital Universitario Virgen de las Nieves.

I also would like to thank clinical collaborators from our University Hospital, including Dr. Angel Concha, the head of the Pathology Dept. who was directly involved in providing cryopreserved tumor tissues of different origin, for the productive cooperation that we have had for many years in

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I want to highlight the period I spent as a postdoctoral fellow in the London Hospital Medical College under the supervision of Dr. Hilliard Festenstein.

He helped me to start a new project in his lab typing H-2 antigens in mouse tumors in 1974–1975. I learned immunogenetics of the H-2 system and applied this knowledge to the altered HLA expression observed in tumor cells. This was the beginning of my journey in the field of “MHC and cancer.” Drs. Dominique Charron (Paris) and Renee Fauchet (Nantes) introduced for the first time the “HLA and cancer” component in the XII International Histocompatibility workshop in 1996. I would also like to thank the Spanish Medical Research Council (Fondo de Investigaciones Sanitarias, FIS) for financing our research since 1981 and “Ramon Areces Foundation” in Spain for financing the “HLA and Cancer” meetings organized in Granada in 1998 and 2011. I would like to thank many different PhD and postdoctoral students that worked in our group at Hospital Universitario Virgen de las Nieves in Granada since 1981: Javier Martin, Concha Delgado, Rosario Oliva, Susana Pedrinaci, Maria Luisa Garrido, Antonio Garrido, Abelardo Caballero, Maximino Redondo, Julia Canton, Alfonso Serrano, Rosa Mendez, Jose Maria Romero, Monica Bernal, Teresa Rodriguez, Francisco Perea, Luis Miguel Real, Rafael and Javier Carretero, Irene Romero, Cristina Garrido, Ana Belen del Campo, Isabel Maleno, and Greta Garrido from the Molecular Immunology Institute of Havana, Cuba. All made important discoveries published in leading international journals. I would specifically thank Dr. Monica Bernal for her help in making different figures of this book, Dr. Fran Perea for the images of tissue immunohistochemistry, Dr. Teresa Rodriguez and Maria Jose Olivares for helping me with the reference list, and Drs. Natalia Aptsiauri, Francisco Ruiz-Cabello, and Angel Garcia Lora for the critical review of the book. Finally, I would like to thank my family, my wife, Antonia Collado, who has been always by my side in difficult moments and helped me with my research for many years working in the Research Unit of our Hospital, and my three daughters, Pilar, Carolina, and Nona, who missed me many times when I was travelling to different places and meetings.

This book summarizes the progress made in the field of “MHC and Cancer Immune Escape” and the contributions made by many scientists all over the world. Nevertheless, there is still a long way before we fully understand the “stealth technology” used by cancer cells to escape and find new methods to fight it that can be applied in the clinic. MHC was discovered in experiments with tumor transplantation in mice. The impact of HLA tissue typing in human transplantation helped to improve our knowledge about this complex genetic system. Now MHC/HLA returns to cancer owing its important role in tumor rejection and escape. The MHC system did not evolve to fight cancer but is no doubt playing a pivotal role. Perhaps, MHC is now “repaying” to cancer cells for being discovered. It is likely that “MHC and cancer” will be travelling together for the years to come.

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# Introduction

1

## Abstract

This chapter focuses on the discovery of the Major Histocompatibility Complex (MHC) in mice (H-2) and in humans (HLA), and on the role played by the International HLA Workshops in the analysis and characterization of this complex genetic system. The early days of Tumour Immunology and the importance of the definition of Tumour Associated Transplantation Antigens (TATA) are also discussed. Today we know that tumour cells can be killed by T lymphocytes by recognizing tumour antigenic peptides presented by MHC molecules and they can also escape this recognition by losing the expression of MHC molecules. This important phenomenon has been profoundly studied for many years both in my lab in Granada and in other laboratories. The results of this research have important implications for the new generation of cancer immunotherapy that boosts T cell responses. A historical perspective of major discoveries is presented in this chapter, with the names of the scientists that have made a significant contribution to the enormous progress made in the field of Tumour Immunology.

## Keywords

MHC · HLA · H-2 · Major histocompatibility complex · HLA heavy chain · Beta2 microglobulin · Tumor immunology · Tumor escape · HLA workshops · Antigen processing

Peter Gorer discovered the Histocompatibility system (H-2) in mice in 1935 in experiments with allogeneic tumor transplantation. The key observation was that tumors fail to growth when transplanted into genetically distinct host of the same species. The antibodies generated in these alloimmunizations were used for MHC typing of red blood cells in inbred strains of mice using a complement-dependent cytotoxicity test (Gorer 1936, 1937; Gorer and Mikulska 1954; Gorer and O’Gorman 1956). This test was used years later to discover and define the HLA system in humans by testing leukocytes with alloimmune sera obtained from individuals after blood transfusion (Dausset 1954) and from pregnant women (van Rood 1962). I recommend reading the article “*Seeds of time: Fifty years ago Peter A. Gorer discovered the H-2 complex*” written by Jean Klein (1986), the publication by Bernard Amos on “*Recollections of Dr Peter Gorer*” (1986) and the book “*H-2 antigens: genes, molecules, function*” edited by Shella David (1987) after the meeting he organized in the Jackson Lab in Bar Harbor (Maine, USA) to commemorate the 50th anniversary of the discovery of the H-2 system (see also Snell 1986).

In 1975–1976 mouse tumors were typed for H-2 antigens in the laboratory of Hilliard Festerstein at the London Hospital Medical College using mouse alloantisera, defining private and public H-2 specificities (Garrido et al. 1976, 1977, 1979; Schmidt et al. 1979). The key finding was that the MHC class I profiles