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Federico Garrido

MHC Class-I Loss  
and Cancer  
Immune Escape

 Springer

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## Acknowledgments

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

difficult times; Dr. Miguel Tallada and Dr. Jose Manuel Cozar (Urology Dept.), Drs. Antonio Cueto and Abel Sanchez-Palencia (Thoracic Surgery), Dr. Javier Gutierrez and Dr. Antonio Ferron (General Surgery), Prof. Francisco Esteban and Dr. Jose Salinero (Otorhinolaryngology Dept.), Prof. Alfonso Herruzo (Gynecology Dept.), and Prof. Salvio Serrano (Dermatology), for cooperating with us at different time periods providing fresh tumor tissue samples of different origin; and the pathologist Dr. Miguel Angel Piris from Madrid and the immunologists Dr. Francisco Real and Prof. Miguel Lopez-Botet from Barcelona for helping to design new approaches in the HLA and cancer field.

I must also mention important and diverse international cooperations that we developed over the years starting with the collaboration with Dr. Peter Stern from the Patterson Institute in Manchester, England. We published two highly quoted reviews in 1993 and 1997, which summarize the work carried out in Granada and Manchester in the 1980s and 1990s in relation to HLA expression in human tumors. Dr. Eva Klein from the Karolinska Institute has been interested in this area of research from the very beginning and organized, together with Dr. Hilliard Festenstein from the London Hospital, the first meeting on "Histocompatibility Antigens in Tumors" that took place in Granada in 1985 (see *J of Immunogenetics* Vol.13, n°2/3, 1986). Drs. Klass Karre and Hans-Gustaf Ljunggren from the same institution collaborated with us in defining the complexity of the different clones of the mouse GR9 fibrosarcoma. Dr. Soldano Ferrone, a pioneer in the HLA and cancer field, collaborated with us when he was working in New York State, in Pittsburg, and later in Harvard University in Boston. Dr. Francesco Marincola at the NIH (USA) helped us to analyze in detail progressing and regressing metastatic lesions in mixed responder melanoma patients. Together with Dr. Marcel Tilanus and Manita Feenstra from Utrecht, we developed novel techniques to define HLA haplotype losses in human tumors and participated in the HLA workshops. With another leading scientist in our field, Dr. Barbara Seliger from Halle in Germany, we collaborated in the investigations of "the antigen presentation machinery" in tumor cells. I have to mention an important collaboration with Drs. Dirk Schadendorf and Annette Paschen (Mannheim and Essen) in defining new molecular mechanisms responsible for HLA alterations in melanoma. With Dr. Gustav Gaudernak and his team at the Norwegian Radium Hospital in Oslo, we have a long-term collaboration studying HLA class I loss in tumor immune escape and cancer progression. Dr. Thierry Boon and Pierre Coulie from the Ludwig Institute in Brussels, who pioneered the identification of tumor antigens recognized by T lymphocytes, cooperated with us in defining HLA-I-associated tumor immune escape mechanisms in patients receiving peptide immunotherapy. With Drs. Alex Knuth (Mainz), Catia Traversari (Milan), and Jesper Zeuthen (Copenhagen), we worked closely defining new molecular mechanisms of HLA alteration in melanoma. With Drs. Graham Pawelec (Tubingen) and Steve Marsh (London), we collaborated in an EU project in which a European melanoma cell bank (ESTADB) has been developed.

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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