Publicado en Nature, Junio 2021

Tissue-resident macrophages provide a pro-tumorigenic niche to early NSCLC cells

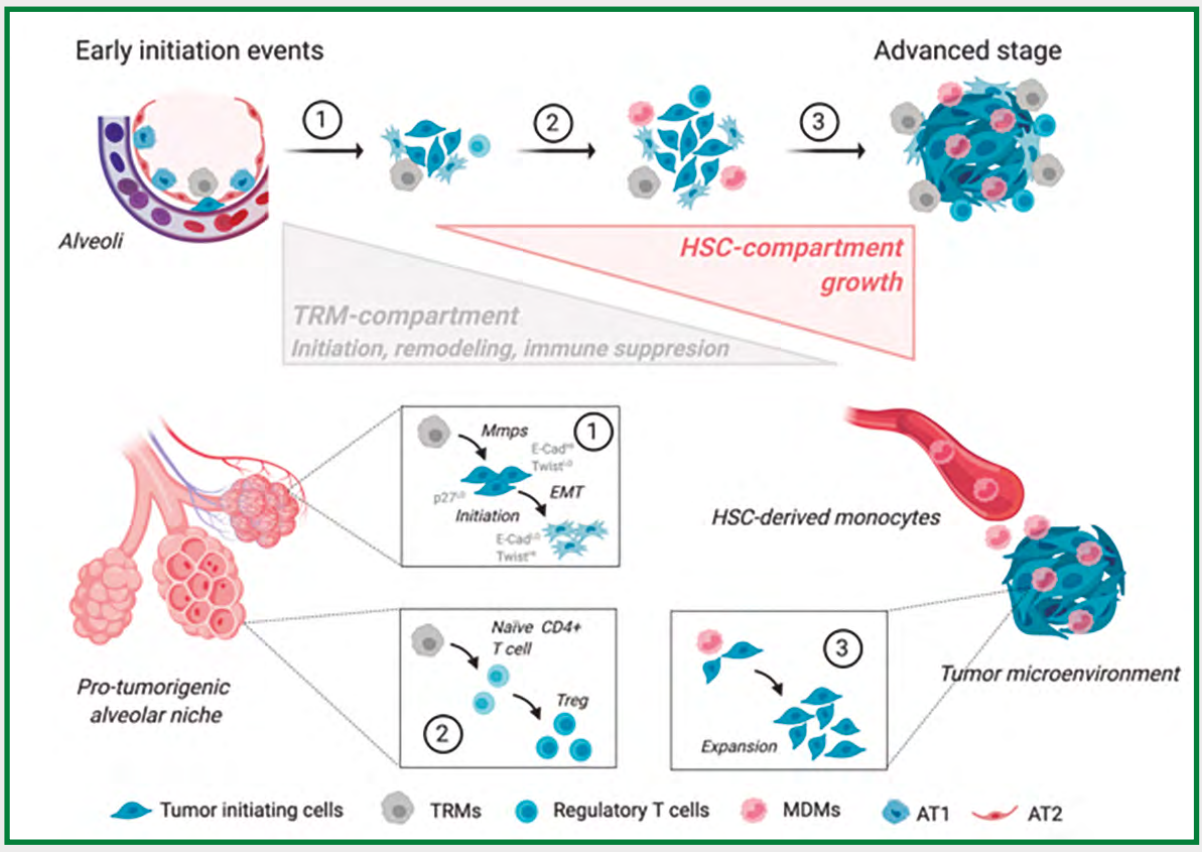
María Casanova-Acebes[1,2,3,19†]; Erica Dalla[4,5,6,7,21]; Andrew M. Leader[1,2,3,21]; Jessica LeBerichel[1,2,3,21]; Jovan Nikolic[8]; Blanca M. Morales[9]; Markus Brown[9]; Christie Chang[1,2,3]; Leanna Troncoso[1,2,3]; Steven T. Chen[1,2,3]; Ana Sastre-Perona[10,11] Matthew D. Park[1,2,3]; Alexandra Tabachnikova[1,2,3]; Maxime Dhainaut[2,3,12]; Pauline Hamon[1,2,3]; Barbara Maier[1,2,3,20]; Catherine M. Sawai[13]; Esperanza Agulló-Pascual[14]; Markus Schober[10]; Brian D. Brown[2,3,12,17]; Boris Reizis[15]; Thomas Marron[1,2,3,4,16]; Ephraim Kenigsberg[2,17]; Christine Moussion[9]; Philippe Benaroch[8]; Julio A. Aguirre-Ghiso[1,2,3,4,5,6,7,22]; Miriam Merad[1,2,3,18,22†]

[1]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]Division of Hematology and Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [5]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]Black Family Stem Cell Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [7]Department of Otolaryngology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [8]Institut Curie, PSL Research University, INSERM U932, Paris, France; [9]Department of Cancer Immunology, Genentech, South San Francisco, CA, USA; [10]The Ronald O. Perelman Department of Dermatology, New York University Grossman School of Medicine, New York, NY, USA; [11]Experimental Therapies and Novel Biomarkers in Cancer, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain; [12]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [13]INSERM U1218 ACTION, University of Bordeaux, Bordeaux, France; [14]Microscopy CoRE, Dean's CoREs, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [15]Department of Pathology, New York University Grossman School of Medicine, New York, NY, USA; [16]Institute of Thoracic Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [17]Icahn Genomics Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [18]Human Immune Monitoring Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [19]Present address: Cancer Immunity Laboratory, Molecular Oncology Program, Spanish National Cancer Centre, Madrid, Spain; [20]Present address: CeMM, Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria; [21]These authors contributed equally: Erica Dalla, Andrew Leader, Jessica LeBerichel; [22]These authors jointly supervised this work: Julio A. Aguirre-Ghiso, Miriam Merad; †e-mail: mcasanova@cnio.es; miriam.merad@mssm.edu

PMID: 34135508 DOI: 10.1038/s41586-021-03651-8

Macrophages are the largest immune cell compartment of solid tumor lesions. Through their ability to promote tissue remodeling, cell clearance, antigen processing and presentation and production of immunomodulatory cytokines, macrophages play a key role in shaping the composition of the tumor microenvironment (TME), the modulation of tumor innate and adaptive immunity, and the response to cancer immunotherapy. Because of their critical roles, macrophages are an important target for cancer treatment. However, modulating tumor-associated macrophages has proved extremely difficult. This is particularly true for human macrophages, whose biology has primarily been studied using human monocyte-derived macrophages generated *in vitro*. This definition hence, remains incomplete and has ignored the tissue resident-macrophage (TRMs) lineage, which arise from embryonic precursors

that are recruited to tissues prior to birth. This is in contrast to monocyte-derived macrophages (MDMs), which arise from adult hematopoietic stem cells and are recruited to tissues in response to injury. Using fate-mapping approaches, we discovered that clusters of TRMs and MDMs co-existed in KRAS^{G12D}/p53null (KP) lung tumors and remained distinct even in the most advanced tumor lesions. Longitudinal tumor imaging revealed that TRMs interact with tumor cells to promote tumor invasiveness before redistributing around the tumor lesions. Unbiased scRNASequencing of fate-mapped tumor-associated macrophages and fresh patient biopsies, revealed the presence of major discrete macrophage populations that differ in origin, and have a distinct temporal and spatial distribution in the TME. Ablating TRMs while sparing adult MDMs, significantly reduced regulatory T cell numbers and altered their immunosuppressive phenotype, promoted the accumulation of CD8+T cells, and reduced tumor invasiveness and growth. Our study underlines the key contribution of TRMs in providing an ideal niche for early cancer progression, highlighting TRMs as a potential target for the prevention or treatment of early NSCLC lesions.



Por María Casanova Acebes, PhD.

Grupo Inmunidad del Cáncer Centro Nacional de Investigaciones Oncológicas, CNIO. mcasanova@cnio.es. Teléfono +34 91 732 8000 (ext. 3570) Melchor Fernández Almagro, 328029 Madrid, España www.cnio.es. fcracfc@gmail.com