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Type I IFNs promote cancer cell stemness by triggering the epigenetic regulator KDM1B

Martina Musella[1], Andrea Guarracino[2,3], Nicoletta Manduca[1], Claudia Galassi[1,4], Eliana Ruggiero[5], Alessia Potenza[5], Ester Maccafeo[1], Gwenola Manic[6,7], Luca Mattiello[6,7], Sara Soliman Abdel Rehim[2,6], Michele Signore[8], Marco Pietrosanto[2], Manuela Helmer-Citterich[2], Matteo Pallocca[9], Maurizio Fanciulli[10], Tiziana Bruno[10], Francesca De Nicola[10], Giacomo Corleone[10], Anna Di Benedetto[11], Cristiana Ercolani[11], Edoardo Pescarmona[11], Laura Pizzuti[12], Francesco Guidi[1,13], Francesca Sperati[14], Sara Vitale[1], Daniele Macchia[15], Massimo Spada[15], Giovanna Schiavoni[16], Fabrizio Mattei[16], Adele De Ninno[17], Luca Businaro[17], Valeria Lucarini[18], Laura Bracci[16], Eleonora Aricò[19], Giovanna Zicchedu[20], Francesco Facchiano[16], Stefania Rossi[16], Massimo Sanchez[21], Alessandra Boe[21], Mauro Biffoni[16], Ruggero De Maria[1,13,23] ✉, Ilio Vitale[6,7,23] ✉ and Antonella Sistigu[1,13,22,23] ✉

Cancer stem cells (CSCs) are a subpopulation of cancer cells endowed with high tumorigenic, chemoresistant and metastatic potential. Nongenetic mechanisms of acquired resistance are increasingly being discovered, but molecular insights into the evolutionary process of CSCs are limited. Here, we show that type I interferons (IFNs-I) function as molecular hubs of resistance during immunogenic chemotherapy, triggering the epigenetic regulator demethylase 1B (KDM1B) to promote an adaptive, yet reversible, transcriptional rewiring of cancer cells towards stemness and immune escape. Accordingly, KDM1B inhibition prevents the appearance of IFN-I-induced CSCs, both in vitro and in vivo. Notably, IFN-I-induced CSCs are heterogeneous in terms of multidrug resistance, plasticity, invasiveness and immunogenicity. Moreover, in breast cancer (BC) patients receiving anthracycline-based chemotherapy, KDM1B positively correlated with CSC signatures. Our study identifies an IFN-I → KDM1B axis as a potent engine of cancer cell reprogramming, supporting KDM1B targeting as an attractive adjunctive to immunogenic drugs to prevent CSC expansion and increase the long-term benefit of therapy.

CSCs, also known as tumor-initiating or tumor-propagating cells, are a relatively rare stem-like cell subpopulation within the tumor capable of self-renewal and multilineage differentiation, and responsible for tumor initiation, progression, spreading and therapy resistance[1,2]. Mounting evidence indicates that CSCs can evolve over space and time leading to a high degree of genotypic, phenotypic and functional heterogeneity[2,3]. Along with this, it is emerging that non-CSC subsets can adapt to the changes in the tumor microenvironment (TME), undergoing cell reprogramming and (re)generating CSCs[2].

Epigenetic dysregulations critically affect cancer–immune cell interactions and coevolution during disease onset, progression and response to therapy by influencing cellular states and fates[4]. Not surprisingly given their role in normal stem cell maintenance, epigenetic mechanisms have also been involved in CSC preservation[5]. This feature, together with the inherent reversibility of epigenetic modifications, makes the use of epigenome-targeting drugs (epidrugs) a unique opportunity to rationally target CSCs in combination with conventional therapies[4,6–9].

One key concept in tumor immunology is that some chemotherapeutics, including (but not limited to) anthracyclines (for example, doxorubicin, DOX), oxaliplatin (OXP) and cyclophosphamide[10,11] induce cancer immunogenic cell death (ICD), a form of regulated cell death that initiates adaptive immune responses by the emission

[1]Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy. [2]Department of Biology, University of Rome 'Tor Vergata', Rome, Italy. [3]Genomics Research Centre, Human Technopole, Milan, Italy. [4]Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, USA. [5]Experimental Hematology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy. [6]Italian Institute for Genomic Medicine (IIGM), Candiolo, Italy. [7]Candiolo Cancer Institute, FPO - IRCCS, Candiolo, Italy. [8]RPPA Unit, Proteomics Area, Core Facilities, Istituto Superiore di Sanità, Rome, Italy. [9]UOSD Clinical Trial Center, Biostatistics and Bioinformatics, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [10]SAFU Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [11]Pathology Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [12]Division of Medical Oncology 2, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [13]Fondazione Policlinico Universitario 'A. Gemelli' - IRCCS, Rome, Italy. [14]UOSD Clinical Trial Center, Biostatistics and Bioinformatics, IRCCS San Gallicano Dermatological Institute, Rome, Italy. [15]Center of Animal Research and Welfare, Istituto Superiore di Sanità, Rome, Italy. [16]Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy. [17]Institute for Photonics and Nanotechnologies, Italian National Research Council, Rome, Italy. [18]Department of Paediatric Haematology/Oncology and of Cell and Gene Therapy, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. [19]FaBioCell, Core Facilities, Istituto Superiore di Sanità, Rome, Italy. [20]Oncogenomics and Epigenetics, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [21]Cytometry Unit, Core Facilities, Istituto Superiore di Sanità, Rome, Italy. [22]Tumor Immunology and Immunotherapy Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [23]These authors jointly supervised this work: Ruggero De Maria, Ilio Vitale, Antonella Sistigu. ✉e-mail: ruggero.demaria@unicatt.it; ilio.vitale@gmail.com; antonella.sistigu@unicatt.it

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