Global hyperactivation of enhancers stabilizes human and mouse naive pluripotency through inhibition of CDK8/19 Mediator kinases

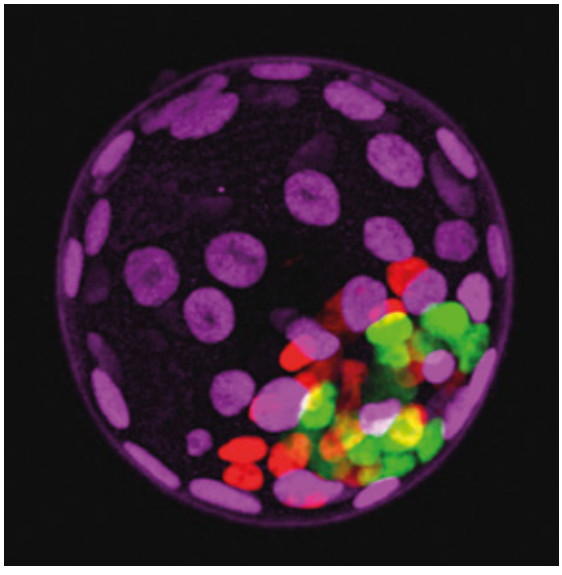
Cian J. Lynch[1,2], Raquel Bernad[1,2], Ana Martínez-Val[1], Marta N. Shahbazi[3,4], Sandrina Nóbrega-Pereira[5], Isabel Calvo[1,2], Carmen Blanco-Aparicio[1], Carolina Tarantino[6], Elena Garreta[6], Laia Richart-Ginés[7], Noelia Alcazar[1,2], Osvaldo Graña-Castro[1], Gonzalo Gómez-Lopez[1], Irene Aksoy[8], Maribel Muñoz-Martín[1,2], Sonia Martinez[1], Sagrario Ortega[1], Susana Prieto[9], Elisabeth Simboeck[9], Alain Camasses[9], Camille Stephan-Otto Attolini[2], Agustin F. Fernandez[10], Marta I. Sierra[10], Mario F. Fraga[10], Joaquin Pastor[1], Daniel Fisher[9], Nuria Montserrat[6,11,12], Pierre Savatier[8], Javier Muñoz[1], Magdalena Zernicka-Goetz[3,13] and Manuel Serrano[1,2,12]

Cell plasticity is a property by which a cell can acquire different and reversible identities. This is essential for embryonic development and is also exploited in several pathologies including cancer, as tumor cells use this property to evade therapy and colonize distant organs. Pluripotent stem cells (PSCs) can transit between different cell plasticity states in vitro, reflecting developmental changes in the early embryo. Until now, PSCs could be stabilized in the so called naïve pluripotent state by methods that include inhibition of external differentiation stimuli, particularly FGF–MEK signaling.

In this work, the authors showed that multiple features of the naïve state in human and mouse PSCs can be recapitulated solely by chemical inhibition of the CDK8 and CDK19 kinases. Mechanistically, inhibition of CDK8/19 removes their ability to repress the Mediator complex, which increases the recruitment of RNA polymerase II to promoters and enhancers and stabilizes the naïve gene expression program.

This groundbreaking study revealed for the first time that internal regulation of the profound mechanisms that regulate gene expression programs can drive naïve pluripotency in stem cells and inhibition of the CDK8/19 kinases is key to this process. These principles may apply to other contexts of cellular plasticity and have future implications in regenerative biology and cancer.

This work was headed by the laboratory of Dr. Manuel Serrano at IRB, Barcelona, in collaboration with researchers from several international centres, including the participation of Sandrina Nóbrega Pereira from the Department of Medical Sciences & iBiMED, University of Aveiro, and was published in the prestigious journal Nature Cell Biology in October 2020.



1 – Spanish National Cancer Research Centre (CNIO), Spain
2 – Institute for Research in Biomedicine (IRB Barcelona), Institute of Science and Technology (BIST), Spain
3 – Department of Physiology, Development and Neuroscience, University of Cambridge, UK
4 – MRC Laboratory of Molecular Biology, Cambridge, UK
5 – Department of Medical Sciences & iBiMED, University of Aveiro, Portugal
6 – Institute for Bioengineering of Catalonia (IBEC), BIST, Spain
7 – Institut Curie, France
8 – Stem Cell and Brain Research Institute, University Lyon, France.
9 – IGMM, University of Montpellier, France
10 – Nanomaterials and Nanotechnology Research Center, Universidad de Oviedo, Spain
11 – Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina, Spain
12 – Catalan Institution for Research and Advanced Studies (ICREA), Spain
13 – Division of Biology and Biological Engineering, Caltech, Pasadena, CA, USA

FIGURE 1

Capturing naïve stem cell pluripotency with CDK8/19 kinase inhibitors. Mouse blastocyst at embryonic day E3.5-4.5 stained for the pluripotency markers GATA6 (red), NANOG (green) and CDX2 (magenta). Photo courtesy of Cian J. Lynch, IRB Barcelona, Spain.