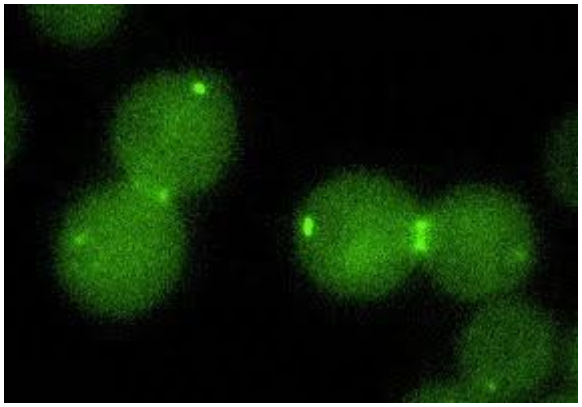
CELL CYCLE CONTROL
DAVID GARCIA QUINTANA



PROFILE

- Professor Agregat / Associate Professor.

- PhD, Universitat Autonoma de Barcelona, 1994.
- World Health Organization International Agency for Research on Cancer Postdoctoral Fellow, 1996-1997.
- Research Fellow, Harvard Medical School, 1996-1999.
- American Cancer Society Senior Postdoctoral Fellow, 1998-1999.
- Research Fellow, Cancer Research UK London Research Institute, 2000-2002.
- Ramon y Cajal Scientist 2003-2008.
- Project Evaluator ANEP / AEI Spanish National Funding Agencies, 2003-present.

Promotion of former PhD students:

- Anna Travesa, Project Scientist, University of California San Diego.
- Angel Guerra-Moreno, Postdoctoral Fellow, Harvard Medical School.
- Gloria Palou, Postdoctoral Fellow, MRC Clinical Sciences Centre, London.
- Fanli Zeng, Research Associate, Peking University.
- Alba Duch, Postdoctoral Fellow, Universitat Pompeu Fabra, Barcelona.
- Asrar Malik, Postdoctoral Fellow, University of Virginia.
- Roger Palou, Postdoctoral Fellow, University of Montreal.
- Ping Ren, Associate Postdoctoral Fellow, Yale University.
- Nathalie Guibourt, Research Scientist, Celgene Institute of Translational Research Europe.

RESEARCH

RESEARCH INTERESTS/STRATEGIC OBJECTIVES/MAIN RESEARCH LINES

Cell cycle control pathways involved in the protection of genomic integrity, proliferation and cancer Our interest is to identify novel cell cycle control elements and pathways involved in the protection of genomic integrity and the regulation of cell proliferation. An area of activity in our lab focuses on the DNA damage response (DDR), a surveillance mechanism that responds to insults that threaten DNA replication. In that event, the DDR blocks mitosis to avoid the segregation (mitotic anaphase) of damaged, incompletely replicated chromosomes to the two future daughter cells. Loss of such control leads to aneuploidy and genomic instability, the driving force of malignant transformation and progression. The DDR constitutes an anti-cancer barrier in early human tumorigenesis. We have recently identified (Plos Genetics, 2015) that 3 different pathways under the DDR kinase Mec1/ATM/ATR are in place to prevent anaphase in response to DNA damage. Two of them, mediated by Swe1/Wee1 and Rad53/Chk2, redundantly block mitotic Cyclin Dependent Kinase (M-Cdk1). Cdk1 is the engine that drives cell cycle progression, and M-Cdk1 is essential for cells to enter anaphase. Our results unveil an unsuspected implication of Rad53 in the control of Cdk1 activity, and reconcile the long-standing conundrum of Swe1 dispensability.

More recently, we identified that even when cells fail to trigger a full DNA damage response, the so-called Spindle Assembly Checkpoint (SAC) still prevents the segregation of incompletely replicated or damaged chromosomes (Current Genetics, 2017). Derived from such observation, the SAC emerges as an attractive target for anti-tumoral therapy. As many cancer cells are characteristically defective in ATM/ATR signaling, blocking SAC signaling might help as co-adjuvant treatment in therapies based on DNA damaging drugs, selectively pushing malignant cells into aberrant, inviable anaphases.

We also worked to demonstrate a missing prediction required to fully validate the so-called quantitative model of cell cycle regulation by Cyclin Dependent Kinases, put forward by Nobel Laureate Paul Nurse as long back as 1996. There are at least two explanations for how such regulation is achieved. According to one of the visions, cyclins confer intrinsic substrate specificity to the CDK catalytic subunit. Alternatively, the quantitative model proposes that ever-increasing levels of CDK activity are required to trigger cell cycle events from G1 to M. If a

quantitative control prevails, then an early cyclin should trigger latter cycle events if accumulated at high enough levels at the right time and place. We were able to trigger DNA replication overexpressing an hyperstable allele of a G1 phase cyclin fused to a nuclear localization signal, in the absence of S, G2 and M phase Cdk1 activity (Cell Cycle, 2015).

Finally, work is going on in our lab aimed at dissecting the control of cytokinesis, the very last step of cell division, when the mother cell separates into two daughter cells. Normal cells prevent cytokinesis until anaphase is complete (two nuclei fully formed). However, such control is subverted in cancer cells, resulting in aneuploidy and genomic instability. We are currently working to obtain a time-lapse record of cytokinesis through a combination of conditional mutants and fluorescence microscopy.

LAB FEATURED PUBLICATIONS

- Palou G, Palou R, Zeng F, Vashisht AA, Wohlschlegel JA, Quintana DG (2015). Three Different Pathways Prevent Chromosome Segregation in the Presence of DNA Damage or Replication Stress in Budding Yeast. PLoS Genet 11:e1005468.