

# Cell Division and Cancer Group

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Scientific Report 2010 **crío**



Marcos Malumbres

## Group Leader

Marcos Malumbres was born in Tudela, Spain, in 1965. He studied Biology at the *Universidad de Navarra* and then moved to León to characterise the genes and molecular pathways leading to amino acid biosynthesis in bacteria. Marcos obtained his PhD in Molecular Biology at the *Universidad de León* in 1993 and moved to the New York University Medical Center (USA) for his postdoctoral training in collaboration with A. Pellicer (1994-1998). During this period, he focused on the effect of Ras activation in cell cycle control and cell proliferation.

Marcos returned to Spain at the end of 1998 to join M. Barbacid's lab in the then newly created CNIO. His research focused on the generation of mouse models to analyse the *in vivo* role of cyclin-dependent kinases and their inhibitors in cell cycle progression and tumour development. In 2003 he obtained a Staff Scientist position at the *Consejo Superior de Investigaciones Científicas (CSIC)* and in June 2004 he decided to stay at the CNIO to lead the Cell Division and Cancer Group.

Marcos Malumbres has authored more than 80 papers including relevant contributions to understanding the *in vivo* function of key cell cycle regulators and their relevance in cancer therapy. He has also contributed to deciphering the role of microRNAs in tumour development and their putative therapeutic uses in cancer. Malumbres received the Beckman-Coulter Award for Young Scientists in 2005.

## Summary

The Cell Division and Cancer Group is interested in understanding the relevance of several mitotic regulators not only during the cell cycle but also in physiological processes in different tissues. We are using mouse models with genetic alterations in several mitotic regulators and microRNAs to gain insight into their *in vivo* role and potential use in cancer therapy.

Our research also focuses on the regulatory mechanisms that control asymmetric cell division in progenitor/stem cells and their functional relevance in development, tissue homeostasis and cancer.

## Strategic Goals

- Understand the basic control mechanisms of the mammalian cell cycle
- Characterise the physiological consequences as well as potential therapeutic values of cell cycle deregulation in animal models
- Characterise the function of microRNAs in cell biology and tumour development
- Understand the functional relevance of cancer stem cells and their proliferative control





**Staff scientists:** Guillermo de Cárcer and Ignacio Pérez de Castro. **Post-doctoral fellows:** María J. Bueno, Massimo Chiesa, Pei Pei Gan, Carlos I. Michel (since June) and Ruth Sánchez. **Graduate students:** Cristina Aguirre, Manuel Eguren, Alejandra González (since October), María Guillaumot, Eusebio Manchado, Víctor Quereda, Marianna Trakala and Paulina A. Wachowicz (until June). **Technicians:** Beatriz Escobar, Marta Gómez de Cedrón and Susana Temiño (until April).

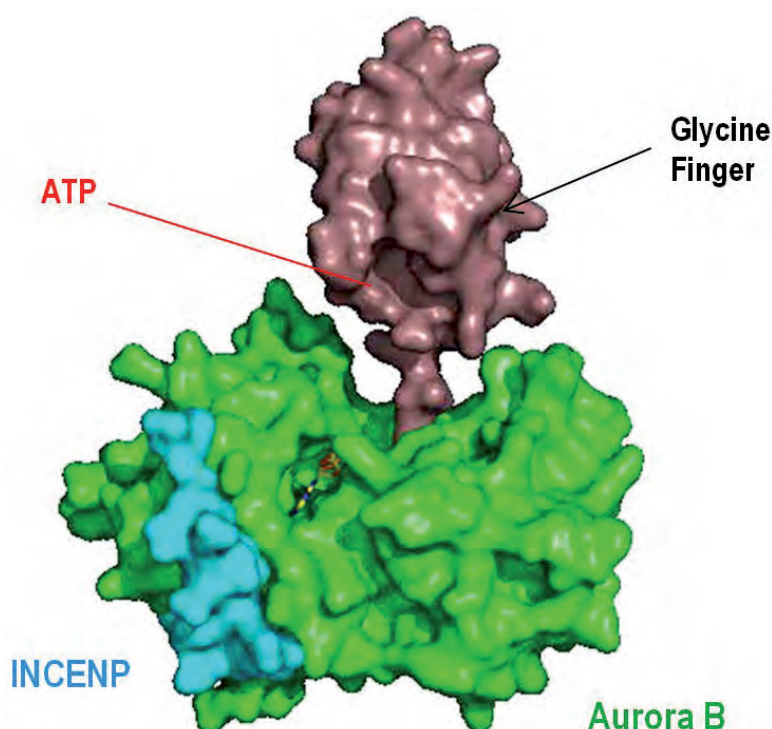
## Highlights

### Modelling the function of mitotic kinases and phosphatases

We have focused on the major cell cycle kinases that regulate progression through mitosis. All three Aurora kinases, A, B and C, contain a SUMOylation motif highly conserved through evolution. In collaboration with W.C. Earnshaw's group (Edinburgh, UK) and the Macromolecular Crystallography Group (CNIO) we have observed that Aurora A and Aurora B are tagged by different SUMO peptides (Figure 1) and that interference with this

post-translational modification results in defective Aurora function and genomic instability. Genetic ablation of Aurora B results in embryonic lethality after embryo implantation. Aurora C may complement for Aurora B loss during the first embryonic cell divisions or in rescue experiments in culture. We are currently analysing the cellular requirements for these proteins during the spindle assembly checkpoint using conditional knockout cells.

In collaboration with G. Manning at the Salk Institute (San Diego, USA) we have also



**Figure 1:** A model for the modification of Aurora B kinase by SUMO peptides (in collaboration with Guillermo Montoya from the CNIO's Macromolecular Crystallography Group).

identified a fifth member of the Polo-like kinase family in mammals. This protein, Plk5, also contains a Polo-box domain although it is not an efficient kinase *in vitro*. Plk5 is mostly expressed in brain cells and its overexpression interferes with entry into mitosis. In collaboration with the *Hospital Nacional de Paraplégicos* and the *Hospital Virgen de la Salud*, Toledo (Spain), we have demonstrated that Plk5 is necessary for neuronal function and the corresponding gene is epigenetically deregulated in brain tumours.

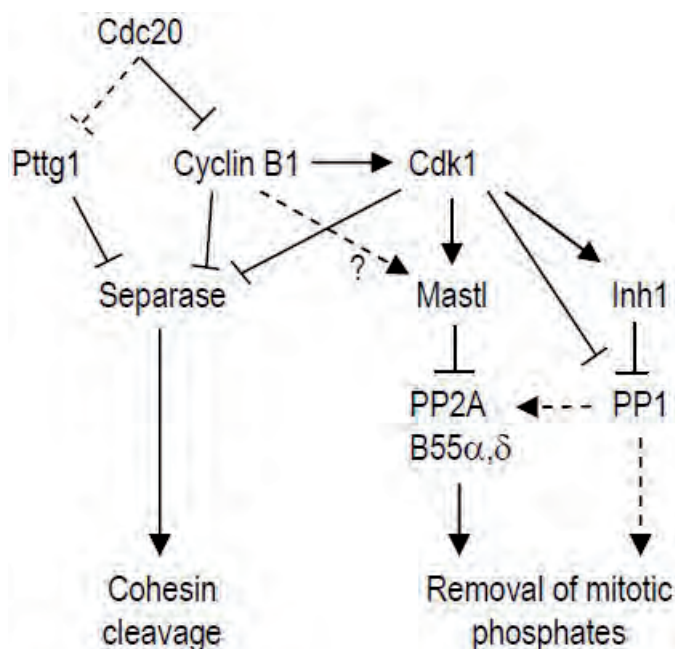
### The anaphase-promoting complex and protein degradation

The Anaphase Promoting Complex (APC/C, or cyclosome) is an E3-ubiquitin ligase whose activity depends on two co-activators: Cdc20 and Cdh1/Fzr1. Along with Marta Cañamero's Comparative Pathology Core Unit (CNIO), S. Moreno's group (*Instituto de Biología Molecular y Celular del Cáncer*, Salamanca) and H. Yamano's group (University College London, UK), we have demonstrated that genetic ablation of Cdc20 results in embryonic lethality at the two-cell stage of embryonic development. Cdc20-null cells arrest in metaphase in accordance with the function of this APC/C cofactor in the metaphase-to-anaphase transition. Cdc20 also appears to play an essential role in adult somatic cells since its acute genetic ablation results in mitotic arrest and proliferative defects *in vivo*. Genetic ablation of Cdc20 results in

metaphase arrest and apoptosis in tumour cells. These Cdc20-null tumours regressed within a few days after loss of Cdc20. This strong effect contrasts with the partial therapeutic benefits of using current mitotic drugs such as Taxol or Plk1 inhibitors in similar assays. The molecular characterisation of Cdc20-null cells has allowed us to uncover a critical function for the PP2A-B55 phosphatase in mitotic exit. During a normal cell cycle, Cdc20 triggers the inactivation of the kinase Mast1, an inhibitor of PP2A, thus resulting in PP2A activation, removal of Cdk-dependent mitotic phosphates and mitotic exit (Figure 2).

### The actin cytoskeleton and tumour development

With the Hereditary Endocrine Cancer Group (CNIO) we have recently characterised the importance of a protein, known as Brick1, in tumour development. The *BRK1* gene encoding Brick1 is located close to the Von Hippel-Lindau (VHL) gene and both of these genes are frequently co-deleted in VHL patients. Interestingly, these patients are protected against renal cell carcinoma. We have recently demonstrated that Brick1 is required for cell transformation and tumour progression due to its critical role in actin dynamics. These data suggest the potential therapeutic uses of inhibiting the actin cytoskeleton in VHL patients that maintain a wild-type *BRK1* gene or other tumour types (Figure 3).

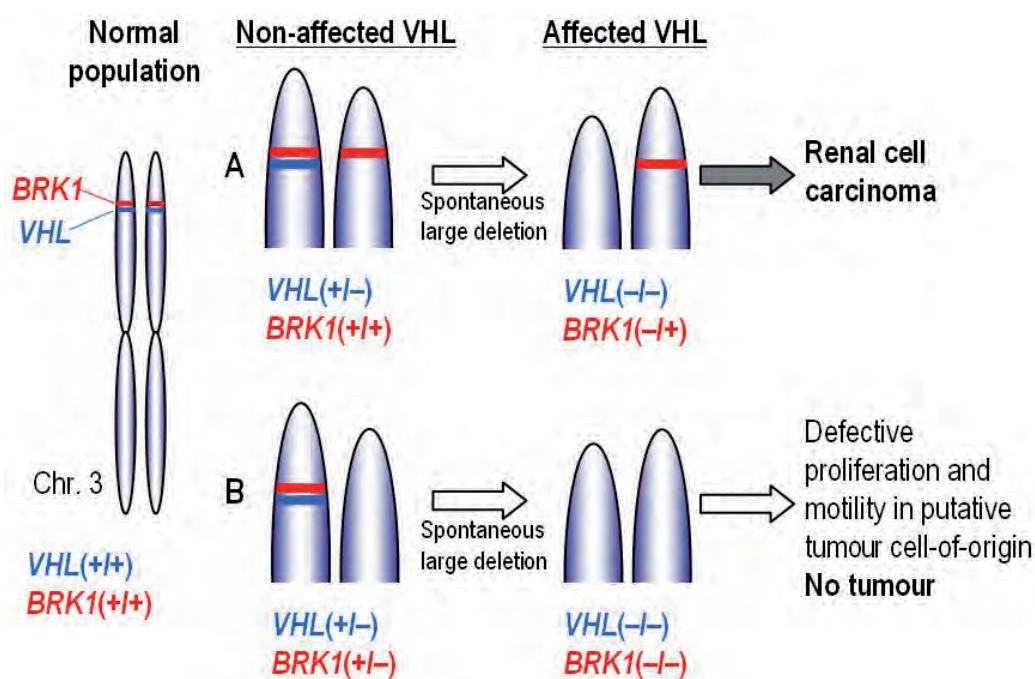


**Figure 2:** A working model for mitotic exit in mammalian cells.

## Control of cell proliferation by microRNAs

We have studied the relevance of microRNAs (miRNAs) in the cell cycle at different levels. We have first analysed the expression of miRNAs in early cell cycle phases and have identified several clusters of miRNAs that are induced by E2F transcription factors during the early phases of the cell cycle. Several of these miRNAs modulate major proliferation pathways by controlling the expression of critical cell cycle regulators

such as cyclins and cyclin-dependent kinases. The induction of these miRNAs prevents replicative stress upon cell cycle entry in the presence of strong mitogenic signals.



**Figure 3:** Schematic representation of the chromosomal location of *BRK1* and *VHL* genes and their relevance in tumour development in VHL patients.

## Publications

Manchado E, Guillamot M, de Cárcer G, Eguren M, Trickey M, García-Higuera I, Moreno S, Yamano H, Cañamero M, Malumbres M (2010). Targeting mitotic exit leads to tumor regression *in vivo*: modulation by Cdk1, Mastl, and the PP2A/B55a,d Phosphatase. *Cancer Cell* 18, 641-654.

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Gurden MD, Holland AJ, van Zon W, Tighe A, Vergnolle MA, Andres DA, Spielmann HP, Malumbres M, Wolthuis RM, Cleveland DW, Taylor SS (2010). Cdc20 is required for the post-anaphase, KEN-dependent degradation of centromere protein F. *J Cell Sci* 123, 321-330.

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