

CELL DIVISION AND CANCER GROUP

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**Plan de Empleo Joven* (Youth Employment Plan)

OVERVIEW

The Cell Division and Cancer Group is interested in deciphering the mechanisms by which cell division and cell proliferation are regulated. During the past few years, we have used different mouse models to understand the relevance of cell cycle regulators, including cell cycle kinases and phosphatases, as well as proteins involved in ubiquitin-dependent degradation, in the control of cell division and tissue physiology. Our interests are: i) to understand the basic control mechanisms that regulate the cell division cycle; ii) to characterise the physiological and therapeutic consequences of cell cycle deregulation; iii) understanding the function of microRNAs in cell biology and tumour development, and iv) to understand how progenitor cells and cancer stem cells control their self-renewal and proliferative properties. As a final goal, we aim to generate information that may be useful for improving therapeutic strategies against cancer cell proliferation.

“In 2016, we investigated the relevance of several mitotic regulators during cancer progression and therapy, with special focus on kinases that are currently under preclinical and clinical evaluation.”

RESEARCH HIGHLIGHTS

Controlling the proper number of cell divisions

The mammalian cell cycle is regulated by at least 2 families of inhibitors, the INK4 and Cip/Kip proteins. While elimination of individual members of these families is a frequent finding in human cancer, the consequences of eliminating this inhibitory mechanism in mammalian cells have not yet been explored. Using a combination of mutant alleles in the mouse, we have now observed that a major physiological function of cell cycle inhibitors is to prevent replicative stress. In a mouse model insensitive to INK4 proteins and deficient in p21^{Cip1} and p27^{Kip1}, we observed that these inhibitors prevent the accumulation of DNA damage due to replicative stress in different tissues including the nervous system. Ablation of these inhibitors prevents mouse development. This effect is most likely due to hyperactivation of cyclin-dependent kinases as the replicative stress can be prevented by slightly inhibiting the enzymatic activity of these proteins (Quereda *et al.*, 2016).

Cell cycle kinases as new targets for cancer therapy

Cell cycle progression is controlled by phosphorylation events and cell cycle kinases are currently the focus of multiple therapeutic strategies. Inhibitors of the Aurora and Polo-like kinases are evaluated in clinical trials with promising results, at least in haematopoietic malignancies. Over the last few years, we have generated mouse models with specific mutations in these kinases in order to understand their roles in different tissues and cell types. Our recent data have uncovered an unexpected function of Polo-like kinase 1 (Plk1) in the cardiovascular system; a role that we are studying in detail in order to understand possible toxicities derived from the use of Plk1 inhibitors in patients.

A relatively new serine/threonine kinase, known as MASTL (or Greatwall in flies and *Xenopus*), has been characterised as a critical node in cell division. We have previously shown that MASTL is essential for mouse embryonic development and cell cycle progression (FIGURE). This is due to mitotic collapse after nuclear envelop breakdown (NEB). MASTL is exported from the nucleus to the cytoplasm in a CRM1-dependent manner before NEB. Once at the cytoplasm, Greatwall inhibits the PP2A-B55 complexes to maintain the mitotic state. These findings have therapeutic implications since MASTL acts by blocking the function of the PP2A phosphatase, a tumour suppressor frequently altered in human cancer. This implies that the inhibition of MASTL could, at the same time, slow down cell division and reactivate tumour suppressor PP2A, a protein capable of inhibiting many of the oncogenic molecular pathways involved in cancer development.

Over the past few months, we have tested this hypothesis by studying the relevance of MASTL in tumour cell proliferation and its possible use as a cancer target. In collaboration with Miguel Quintela's Group at the CNIO and Carlos Caldas at Cancer Research UK, we analysed MASTL expression in breast cancer. Our data suggest that this protein is overexpressed in a significant number of hormone-positive and -negative tumours and correlates with poor prognosis. In collaboration with researchers at Pfizer, we used different RNAi and CRISPR techniques to analyse the effect of MASTL knockdown or knockout in breast cancer cells both *in vitro* and *in vivo*. These data indicate that some breast cancer cells require MASTL kinase activity for proliferating, suggesting that a subset of breast tumours may benefit from strategies aimed at inhibiting this kinase. We are currently studying the consequences of inhibiting MASTL in the activity of the PP2A phosphatase. Since MASTL specifically inhibits PP2A-B55 complexes, we are also characterising the relevance of the B55 family members present in the human genome. ■

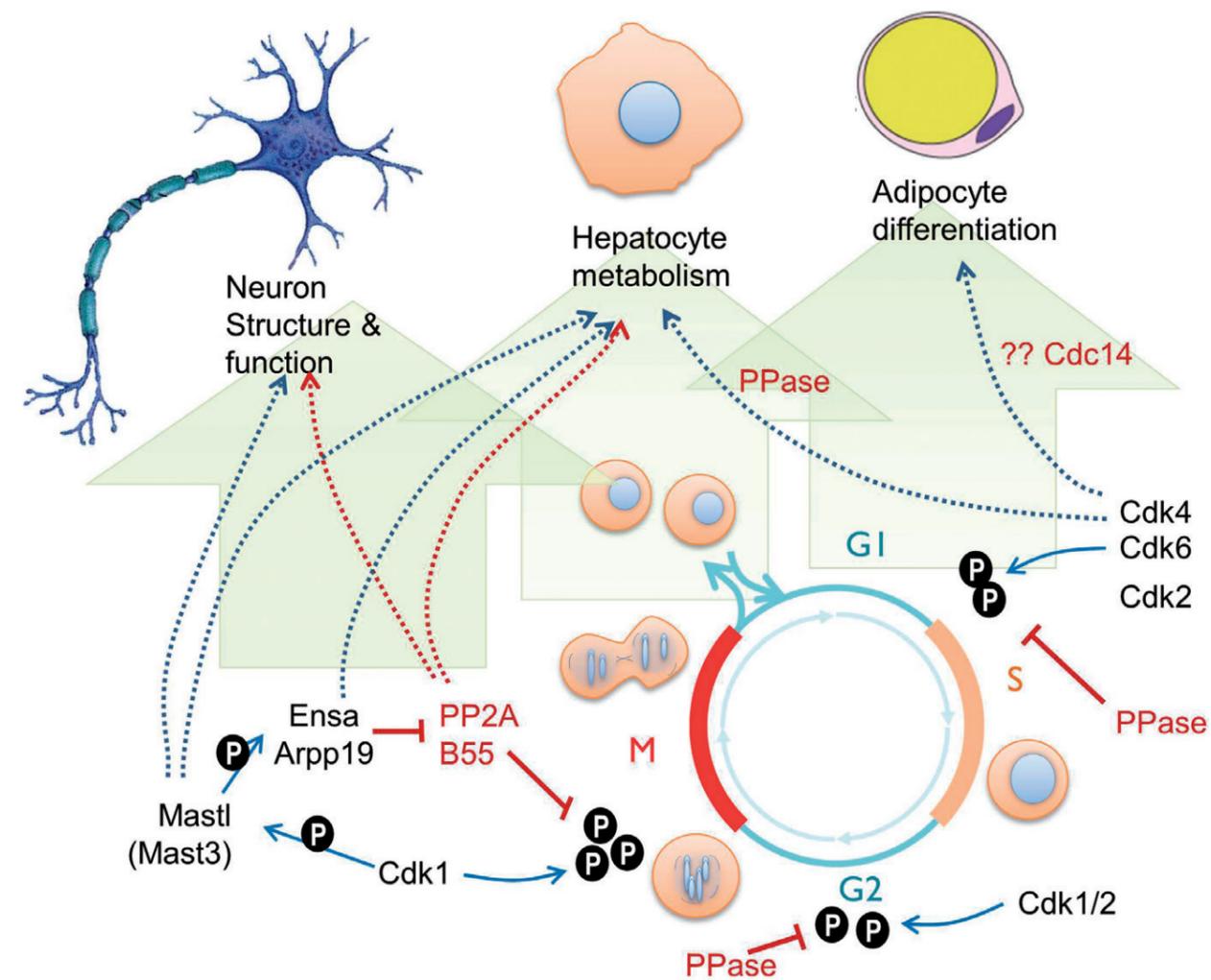


Figure Schematic representation of the control of the mammalian cell cycle by cyclin-dependent kinases (Cdks) and MASTL. MASTL phosphorylates 2 small proteins, known as Ensa and Arpp19, which are both PP2A-B55 inhibitors. The proper balance between cell cycle kinases and phosphatases is crucial, not only for cell cycle progression but also for the structure and function of different tissues.

PUBLICATIONS

- Hydbring P, Malumbres M, Sicinski P (2016). Non-canonical functions of cell cycle cyclins and cyclin-dependent kinases. *Nat Rev Mol Cell Biol* 17, 280-292.
- Malumbres M (2016). CDK4/6 Inhibitors resTore Therapeutic Sensitivity in HER2(+) Breast Cancer. *Cancer Cell* 29, 243-244.
- Shao R, Liu J, Yan G, Zhang J, Han Y, Guo J, Xu Z, Yuan Z, Liu J, Malumbres M, Wan L, Wei W, Zou W (2016). Cdh1 regulates

- craniofacial development via APC-dependent ubiquitination and activation of Goosecoid. *Cell Res* 26, 699-712.
- Blas-Rus N, Bustos-Morán E, Pérez de Castro I, de Cárcer G, Borroto A, Camafeita E, Jorge I, Vázquez J, Alarcón B, Malumbres M, Martín-Cófreces NB, Sánchez-Madrid F (2016). Aurora A drives early signalling and vesicle dynamics during T-cell activation. *Nat Commun* 7, 11389.
- Sobecki M, Mrouj K, Camasses A, Parisis N, Nicolas E, Lières D, Gerbe F, Prieto S, Krasinska L, David A, Eguren M, Birling MC,

- Urbach S, Hem S, Déjardin J, Malumbres M, Jay P, Dulic V, Lafontaine DLJ, Feil R, Fisher D (2016). The cell proliferation antigen Ki-67 organises heterochromatin. *Elife* 5, e13722.
- Quereda V, Porlan E, Cañamero M, Dubus P, Malumbres M (2016). An essential role for Ink4 and Cip/Kip cell-cycle inhibitors in preventing replicative stress. *Cell Death Differ* 23, 430-441.
- Correia NC, Melão A, Póvoa V, Sarmento L, Gómez de Cedrón M, Malumbres M, Enguita FJ, Barata JT (2016). microRNAs

- regulate TAL1 expression in T-cell acute lymphoblastic leukemia. *Oncotarget* 7, 8268-8281.
- Liu J, Wan L, Liu J, Yuan Z, Zhang J, Guo J, Malumbres M, Liu J, Zou W, Wei W (2016). Cdh1 inhibits WWP2-mediated ubiquitination of PTEN to suppress tumorigenesis in an APC-independent manner. *Cell Discover* 2, 15044.

AWARDS AND RECOGNITION

- Elected EMBO Member.