OVERVIEW

The Cell Division and Cancer Group is interested in deciphering the mechanisms by which cell division and cell proliferation are regulated. During the last few years, we have generated and characterised different mouse models in order to understand the relevance of several cell cycle regulators in the control of cell division and tissue physiology; these include cell cycle kinases and phosphatases, and proteins involved in ubiquitin-dependent degradation. Our interests are: i) to understand the basic control mechanisms that regulate the cell division cycles; ii) to characterise the physiological and therapeutic consequences of cell cycle deregulation; iii) characterising the function of microRNAs in cell biology and tumour development, and iv), understanding 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 towards improving therapeutic strategies against cancer cell proliferation.

“In 2015, we investigated the relevance of several mitotic regulators during cancer progression and therapy. We have also described the metabolic changes imposed by microtubule poisons that are used to treat cancer and their therapeutic relevance.”

Marcos Malumbres

Group Leader

Staff Scientists
Mónica Álvarez, Guillermo de Cárcer, Ignacio Pérez de Castro, Eva Portlan

Post-Doctoral Fellows
Begoña Hurtado (since October), Carolina Maestre, María Salazar

Graduate students
Ana F. Balbás-Martín, Elena Domínech (until May), Alejandra González (until January), María Martos, Diego Martínez Alonso (since September), Belén Sanz, María Sanz, Marianna Trakala (until May)

Technicians
David Partida, Elisabet Zapatero (since September) (TS)*

*Titulado Superior (Advanced Degree)
Oncogenic effect of Aurora kinases in cancer

Aurora kinases are enzymes involved in the regulation of mitosis. These proteins are frequently overexpressed in human tumours and are currently considered as putative cancer targets. Yet, the effect of their overexpression in vivo is not well understood. We generated a new mouse model in which endogenous Aurora B can be overexpressed in a conditional manner (González-Loyola et al., 2015). Mice overexpressing this kinase developed a wide variety of tumours. The molecular and cellular characterisation of these tumours suggested that Aurora B overexpression not only induces chromosomal instability, as previously expected, but also results in a dysplastic phenotype, thus contributing to tumour development through multiple mechanisms.

Regulation of the megakaryocyte cell cycle

The cell cycle is widely considered as a universal mechanism for cell proliferation. However, some specialised cells display variant forms of the consensus cell cycle and understanding these differences may be crucial in the design of therapies against specific malignancies. Using mouse models with specific alterations in cell cycle regulators, we studied the reliance of endomitosis and endoreplication; two variants of the canonical cell cycle, in megakaryocytes. These cells undergo multiple rounds of genome amplification without generating daughter cells, thus increasing their ploidy. We have identified several mitotic kinases that, despite being essential for mitotic cell cycles (such as the ones used by cancer cells), are dispensable for the polysynthetic generation of megakaryocytes, thereby providing some new options for leukaemia treatment. Other kinases, such as PKr, are still essential for megakaryocytes and their inhibition leads to thrombocytopenia (Trakala et al., 2015).

Control of cellular metabolism in mitosis

Microtubule poisons, such as taxanes, block mitosis and eventually lead to cell death in a process frequently known as mitotic catastrophe. However, some cells are able to bypass this mitotic arrest and survive, thus contributing to chemo-resistance to those therapies. We have recently observed that mitotic arrest induces an early autophagic flux response, which results in autophagy-dependent mitochondrial degradation and a dramatic energetic deficit (Domènech et al., 2015). The subsequent increase in the AMP:ATP ratio results in the activation of the metabolic sensor AMPK followed by phosphorylation and activation of PFKFB3, an enzyme required for glycolysis. Thus, mitophagy can be considered as a critical effector of the therapeutic effect of mitotic therapies, while both AMPK and PFKFB3 are critical for survival. The manipulation of these molecular routes may have therapeutic benefits in the presence of microtubule poisons (Esteban-Martínez et al., 2015).

Figure 1. Different variants of the mammalian cell cycle are found in mammals. Megakaryocytes normally undergo endomitosis by skipping late mitotic events. In the absence of Cdk1, they undergo repeated S-G phases (endoreplication), whereas the DNA is replicated more than once (re-replication) in the absence of both Cdk1 and Cdk2.