CELL DIVISION AND CANCER GROUP

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OVERVIEW

The Cell Division and Cancer Group is interested in deciphering the mechanisms by which cell division and cell proliferation are regulated in mammalian cells. Our scientific interests are to: i) understand the basic control mechanisms that regulate the cell division cycle; ii) characterise the physiological and therapeutic consequences of cell cycle deregulation; iii) understand self-renewal and pluripotency in stem cell biology and tumour development; and iv) improve the use of old and new targets for cancer therapy. As a final goal, we aim to generate information that will be useful for understanding basic mechanisms of cell function and to improve therapeutic strategies against cancer cell proliferation.

"We have defined the role of mitotic kinases in neural and metabolic disease, and the immune response to chromosomal instability in patients with high tumour susceptibility."

RESEARCH HIGHLIGHTS

Mitotic kinases in developmental diseases

The cell cycle machinery regulates multiple aspects of cell biology, including the balance between proliferation and differentiation in multiple tissues. Several cell cycle kinases, such as polo-like kinase 1 (PLK1), modulate not only centrosome and chromosome biology but also other cellular processes such as the dynamics of the cytoskeleton, cell movements, etc. Our previous work showed critical implications of PLK1 in vascular biology and tumour development. By using gain- and loss-of-function mouse models of PLK1 function, we recently identified a new role for PLK1 in the control of cell fate in neural progenitors during development. Interestingly, centrosomal alterations are thought to be one of the aetiological reasons for primary microcephaly, a defect in which decreased cortex size is accompanied by mental retardation and other symptoms. By combining *Plk1*-mutant alleles with specific mutations in *Cep135* or *Cdk5rap2*, two genes mutated in microcephaly, we described new genetic interactions that lead to defective asymmetry of centrosomal components during the division of neural progenitors, microcephaly, and defective brain development (González-Martínez et al., 2022). Importantly, these phenotypes are also observed after inhibiting PLK1 with small-molecule inhibitors that are currently under evaluation in clinical trials for cancer therapy, raising a note of caution on the possible secondary effects of inhibiting PLK1 in neural progenitor cells.

Links between cell cycle regulation and metabolism

The serine/threonine kinase MASTL (also known as Greatwall) is a critical regulator of mitosis by inhibiting the PP2A phosphatase (2012). We previously reported that loss of MASTL results in mitotic defects such as defective chromosome condensation and segregation errors in mammalian cells. By using a variety of genetic and biochemical models, we have recently reported a mitotic-independent function of the MASTL-PP2A axis in modulating the response to glucose. In conditions of nutrient excess and high mTOR signalling, a negative feedback loop inhibits AKT activity, thus limiting the continuous activation of the AKT-mTOR pathway. In these conditions, MASTL is activated by phosphorylation and inhibits PP2A activity, thereby preventing the function of this phosphatase in allowing the continuous activation of AKT. These observations identify a new layer of control that interconnects a cell cycle module with the negative feedbacks regulating the AKT-mTOR pathway, and suggest the possible use of MASTL inhibition to specifically improve glucose metabolism in specific pathological conditions such as obesity or diabetes.

Chromosomal instability and cancer

Most human tumours display an abnormal number of chromosomes. A few mutations affecting mitotic regulators

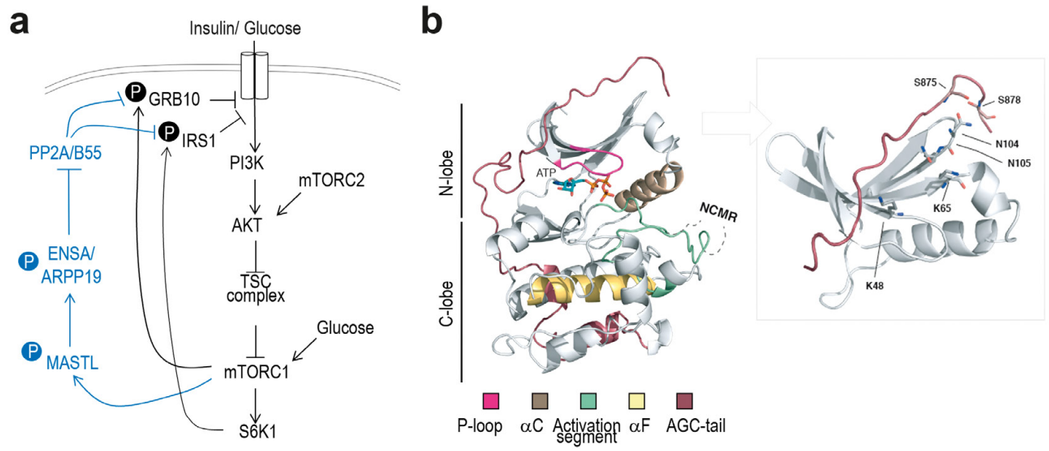

FIGURE 1 A new role for MASTL in the mTOR-AKT feedback loop. (**a**) A model for the new role (in blue) of MASTL in the negative feedback loop that controls AKT activity. (**b**) A homology structural model showing the position of the MASTL S875 residue phosphorylated by mTOR in response to high glucose signalling.

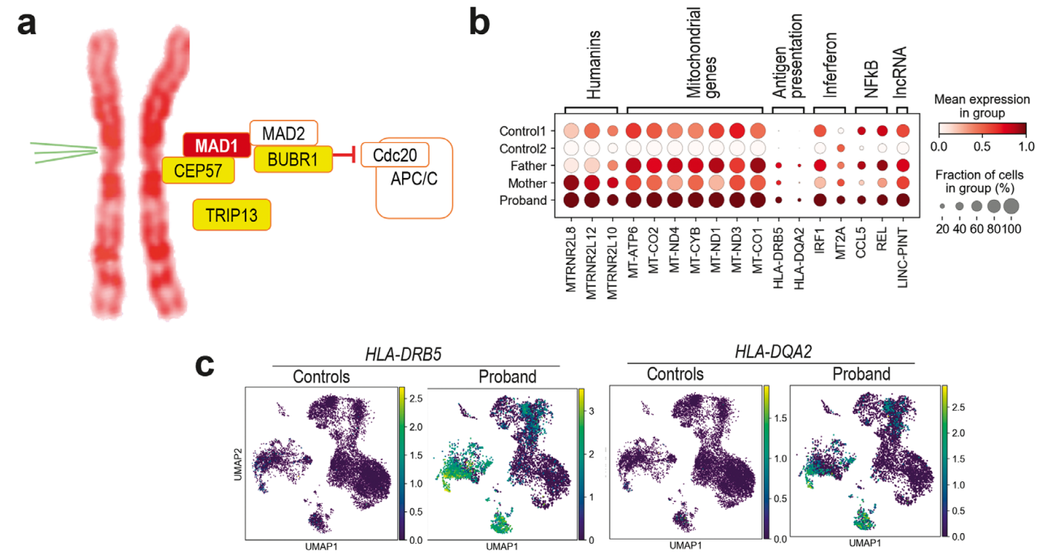

FIGURE 2 MAD1 mutations in a patient with high tumour susceptibility. (**a**) Critical components of the mitotic checkpoint, with genes previously identified in MVA in yellow. (**b**) Enrichment in mitochondrial and immune responses in peripheral blood cells from the proband. (**c**) Single-cell analysis showing upregulation of genes involved in the major histocompatibility complex.

are also detected in familial cancer (Villarroya-Beltri & Malumbres, 2022). In collaboration with the laboratories of Miguel Urioste and Sandra Rodríguez-Perales, we studied the effect of novel mutations in the mitotic checkpoint component MAD1 in a patient with unprecedented levels of tumour susceptibility. Our single-cell data in peripheral blood of the patient suggest that chromosomal instability induced by MAD1 mutations results in an immune response characterised by chronic activation of inflammatory signals (Villarroya-Beltri *et al.*, 2022). These data suggest a new variant of the Mosaic Variegated Aneuploidy (MVA) syndrome with high tumour susceptibility, and an immune response whose detailed analysis may lead to novel strategies for immunotherapy. ■

PUBLICATIONS

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