Cell division: molecular mechanisms and implications in disease

Marcos Malumbres
Centro Nacional de Investigaciones Oncológicas (CNIO).

Cell cycle progression is regulated by several families of protein kinases that not only control the transition between the different phases of the cell cycle, but also prevent genomic instability. Among them, cyclin-dependent kinases (CDKs) are critical engines that promote cell division through the ordered phosphorylation of hundreds, perhaps thousands, of substrates. Recent evidences suggest that specific phosphatase complexes, such as those formed of PP2A and regulatory subunits of the B55 family, counteract CDK-dependent phosphorylation resetting the phosphorylation status of cellular components during mitotic exit. How the balance between kinase and phosphatase activity is established during the different phases of the cell cycle remains unclear, although recent data suggest that an additional family of kinases, represented by Greatwall or MASTL in mammals, is able to inhibit PP2A-B55 activity specifically during mitosis.

Interestingly, the first reference to MASTL in mammals comes from the identification of a mutation present in patients with thrombocytopenia, a disease characterized by reduced number of platelets in the peripheral blood. A putative role for MASTL in these cells is not obvious as platelets are terminally-differentiated enucleated cells. In addition, data in yeast suggest that MASTL orthologues play essential roles in quiescence. Using a variety of mouse models with specific mutations in this kinase, we have explored the physiological in vivo relevance of this kinase in mammals. Our data in specific quiescent or proliferating cells, including platelets, megakaryocytes (cells that undergo aberrant mitotic cycles called endomitosis), or cancer cells suggest that the control of PP2A activity by MASTL may participate in multiple signaling routes and cellular processes in addition to cell division.

ABSTRACT

Since PP2A enzymes are critical enzymes defective in major pathological processes in humans, such as neurodegeneration or cancer, we will discuss the possibilities of manipulating MASTL activity for therapeutic strategies aimed to reactivate cellular phosphatases.