

P029 Control of mammalian development and cell proliferation by the Anaphase Promoting Complex (APC/C) ubiquitin ligase
**Eusebio Manchado, Manuel Eguren
and Marcos Malumbres**

Cell Division and Cancer Group, Centro Nacional de Investigaciones Oncológicas (CNIO) Madrid

Mitotic progression crucially depends on the activation and inactivation of specific cell cycle regulators by protein modifications and degradation. Some of these protein modifications are mediated by critical mitotic kinases, phosphatases and the SUMO machinery. On the other hand, protein degradation during the entry and exit from mitosis is mainly controlled by the Anaphase-Promoting Complex/Cyclosome (APC/C) in association with two adaptor proteins, Cdc20 and Cdh1 (also known as Fzr1 in mammals). These two subunits target specific proteins for ubiquitin-mediated degradation although their specificity for particular substrates is not clear. We have recently generated conditional gene-targeted mice with specific mutant alleles for some mitotic regulators, including the APC/C cofactors Cdc20 or Cdh1. These mitotic regulators are essential for mouse embryonic development although their genetic ablation causes specific phenotypes at different developmental stages. In particular, Cdh1 ablation provokes placental defects accompanied by defective endoreduplication of trophoblast cells. Partial deficiency in Cdh1 also results in tumor formation and hyperproliferation of specific stem cells in adult mice. Complete ablation of Cdh1 has dramatic consequences on the nervous system. Cdc20, on the other hand, is absolutely required for cell divisions during early embryonic development or in adult mice. We are currently analyzing the cell cycle defects induced by the acute elimination of these genes by Cre recombinase under inducible regulation or in specific genetic backgrounds.