PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Cycling without cyclins

ArticleInfo		
ArticleID	:	4995
ArticleDOI	:	10.1186/gb-spotlight-20040824-01
ArticleCitationID	:	spotlight-20040824-01
ArticleSequenceNumber	:	58
ArticleCategory	:	Research news
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2004–8–24 OnlineDate : 2004–8–24
ArticleCopyright	:	BioMed Central Ltd2004
ArticleGrants	:	
ArticleContext	:	130595511

Cathy Holding
Email: cathyholding@aol.com

D-type cyclins and their cyclin-dependent kinases are not essential for cell cycle progression, according to two independent reports in *Cell* this week.

The studies reveal the existence of a previously undescribed mechanism for governing cell cycle progression and for initiating proliferation following mitogenic stimulation.

PeterSicinski's group at Harvard Medical School generated triple knockout mutant mice lacking all three D-type cyclins - cyclin D1, D2, and D3 - while a team at the Centro Nacional de Investigaciones Oncologicas in Spain headed by Marcos Malumbres generated the complementary deletions of cdk6 and cdk4 single and double mutants. Both sets of mice developed normally until the later stages of gestation, after which they died due to severe anemia, among other abnormalities. These observations suggest that CDK6 is required for expansion of certain differentiated compartments, rather than for proliferation of early hematopoietic precursors, the Spanish team writes in their paper. Sicinski's group attributes it to a profound multilineague hematopoietic failure. The teams also examined responses of cell lines generated from the animals to external mitogenic stimuli.

Previous evidence had shown a critical need for the D-type cyclins by proliferating cancer cells. "For this reason, it was suggested that D-type cyclins might be a good target for therapeutic strategies in human cancer," Sicinski told *The Scientist.* However, D-type cyclins are also considered to be required for the proliferation of normal cells, prompting these studies into normal cellular requirments.

"Very surprisingly, we found that these mice developed relatively normally," Sicinski said. "The proliferation of their cells [in vitro] proceeded relatively normally - but these cells remained resistant to oncogenic transformation."

Sicinski said it was a very unexpected discovery that D-type cyclins are not therefore required for normal cell proliferation. "Apparently, they are additional. D-type cyclins are thought to serve as links between the cellular environment and the core cell cycle machinery," he said. Analyzing cells lacking D cyclins revealed that they responded normally to changes in the extracellular environment at the molecular level of the core cell cycle machinery, he said.

And Sicinski said that because D-type cyclins are not critically required due to the existence of alternative pathways, this makes it possible that D-type cyclins may be targeted in human cancers.

"I think overall it's a very interesting story and it really makes us question a lot of things that we thought we knew," said Philipp Kaldis, a principal investigator in the Center for Cancer Research at the National Cancer Institute, Maryland.

However, Kaldis, who was not involved in the study, expressed concern at some results in the cdk knockout paper. First, in order to account for the longer survival of their embryos, Malumbres' team suggested that cdk2 interacts with cyclin D, which, Kaldis said, contradicted the Sicinski group results. In addition, "there is no more cyclin D on cdk2 if you take cdk4 and 6 away," Kaldis said, which Malumbres' group had done with the knockouts. Malumbres said the interaction had been observed in culture, but said it had not been formally demonstrated in embryos.

Further, Kaldis also said he doubted that the Spanish team showed cyclin D2 activity because "nobody has ever shown that before." Malumbres claimed, however, that it has been previously shown in older papers.

Finally, Kaldis noted that the inhibitors p16, p21, and p27 are much lower in the Spanish double knockouts, but levels of p21 and p27 are unchanged in the Sicinski triple knockouts, suggesting contradictory results. Malumbres acknowledged that he could not account for this.

"It's really the hematopoiesis that screws these animals up," Kaldis said, "and if you could rescue that, then probably these animals would be fine."

It also struck John Doonan, researcher in cell and developmental biology at the John Innes Centre, that the types of cell that seem particularly sensitive to the loss of the cyclins and their kinases included blood cell precursors and liver cells - in fact, all types whose proliferation requirements seem to vary quite dramatically depending on the organism's needs, he said. "Maybe the D-cyclins are an extra layer of control that is imposed in these cells that allow them to have a wider range of proliferation responses depending on what needs the organisms has," suggested Doonan, who was not involved in the study.

References

1. M. Malumbres et al., "Mammalian cells cycle without the D-type cyclin-dependent kinases Cdk4 and Cdk6," *Cell,* 118:493-504, August 20, 2004.

2. K. Kozar et al., "mouse development and cell proliferation in the absence of D-cyclins," *Cell*, 118:477-491, August 20, 2004

3. Peter Sicinski, [http://www.dana-farber.org/abo/danafarber/detail.asp?personID=208]

4. Marcos Malumbres, [http://www.cnio.es/ing/index.html]

5. Philipp Kaldis, [http://ccr.cancer.gov/Staff/staff.asp?profileid=5594]

6. John Doonan, [http://www.jic.bbsrc.ac.uk/]