

Start and stop signals of oocyte meiotic maturation

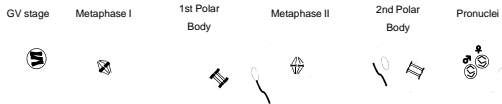


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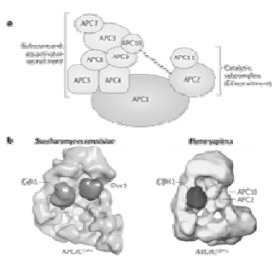


Message of talk

1. Cdh1 - cyclin B1 GV arrest
2. Cdh1 - control of meiosis I
3. Cdh1 - follicle endowment

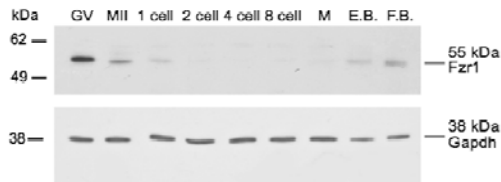


Cdh1= co-activator of Anaphase-Promoting Complex/Cyclosome (APC)

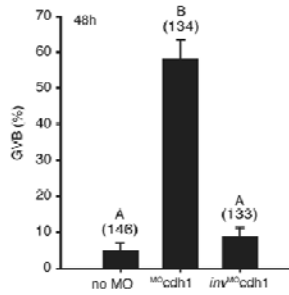


- Multimeric protein complex ~15 subunits
- E3 ubiquitin ligase
- Essential for M-phase, substrates cyclin B1 and securin
- Many other substrates
- Substrates degraded at different times
- Activity regulated by WD40 proteins CDH1 and CDC20

Cdh1 levels high in GV oocytes



Cdh1 needed to maintain GV arrest using antisense morpholino



Reis et al (2006) Nat Cell Biol

Cdh1 knockout is embryonic lethal

Genomic stability and tumour suppression by the APC/C cofactor Cdh1

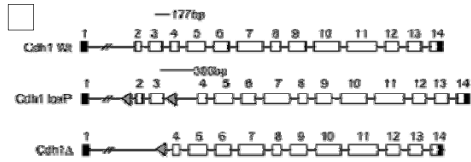
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The anaphase promoting complex or cyclosome (APC/C) is a ubiquitin protein ligase that, together with Cdc20 or Cdh1, targets cell cycle proteins for degradation. APC/C-Cdh1 specifically promotes protein degradation in late mitosis and G1. Mutant embryos lacking Cdh1 die at E9.5-E10.5 due to defects in the endoreplication of hepatoblast cells and placental insufficiency. This lethality is prevented when Cdh1 is expressed in the placenta. Cdh1-deficient cells proliferate inefficiently and accumulate chromosomal and structural abnormalities, indicating that Cdh1 contributes to the maintenance of genomic stability. Cdh1 heterozygous animals show increased susceptibility to spontaneous tumours, suggesting that Cdh1 functions as a haploinsufficient tumour suppressor. These heterozygous mice also show several defects in behaviour associated with increased proliferation of stem cells in the nervous system. These results indicate that Cdh1 is required for preventing unscheduled proliferation of specific progenitor cells and protecting nonstem cells from genomic instability.

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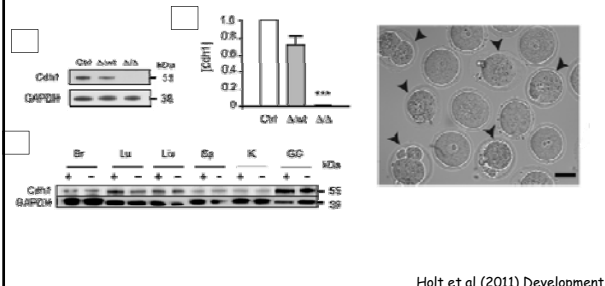
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Cre-loxP to generate an oocyte-specific Cdh1 knockout



Cdh1 loxP x ZP3-Cre KO in oocytes from growing follicles

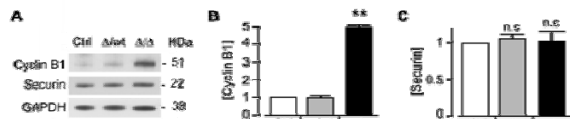
Confirmation of Cdh1 role in GV arrest using oocyte-specific knockout



Holt et al (2011) Development

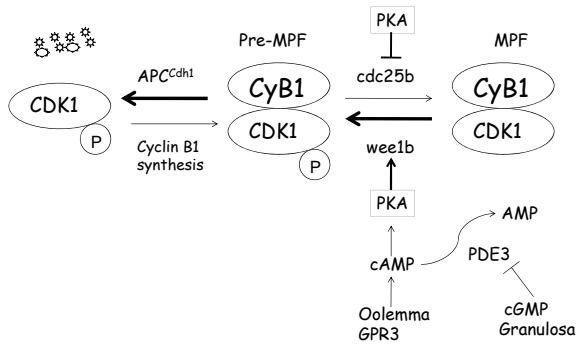
Why is Cdh1 important in GV arrest?

APC^{Cdh1} maintains cyclin B1 levels low
Keeps Cdk1 activity low

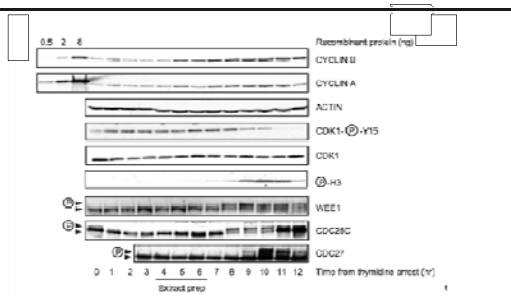


Holt et al (2011) Development

Mechanism of GV arrest

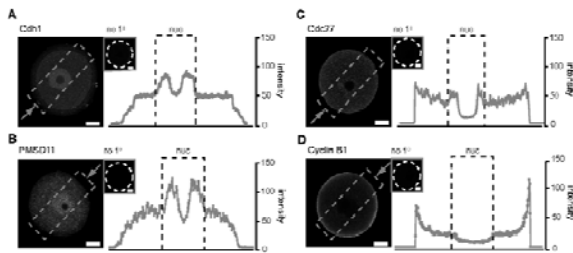


Cyclin B1 levels rise in G2 of the mitotic cell cycle

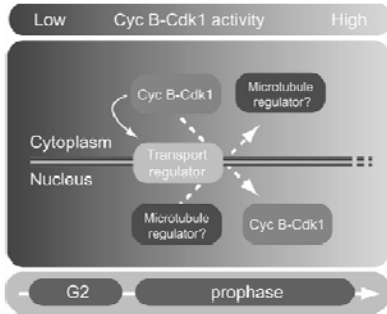


Deibler & Kirschner (2010) Mol Cell

All of the APC^{Cdh1}-proteasomal machinery is in nucleus of GV oocyte

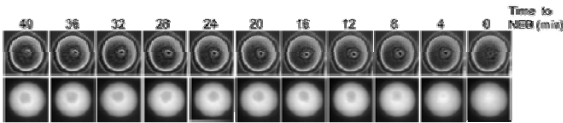


Nuclear cyclin B1-Cdk1 needed for NEB in mitosis

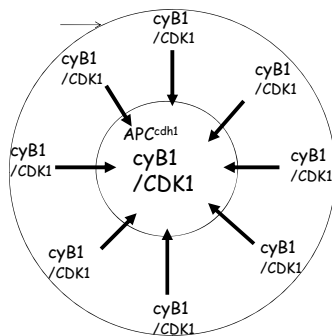


Lindqvist (2010) J Cell Biol

Cyclin B1 translocates to nucleus before NEB/GVB



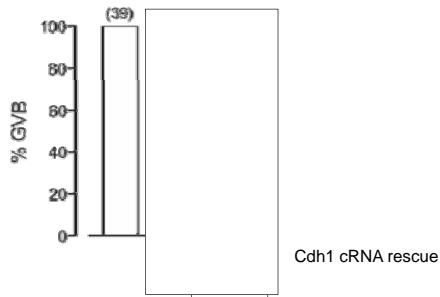
Model: Nuclear APC^{Cdh1} protects GV oocytes from precocious GVB



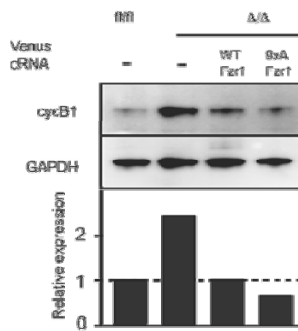
1. Prophase arrest: nuclear APC^{Cdh1} guards against low-level cyB1 entry into nucleus.

2. G2/M: APC^{Cdh1} overcome by enhanced nuclear CDK1/cyB1 entry.

Rescue of GV arrest using Cdh1 enhanced by using nuclear targeted Cdh1



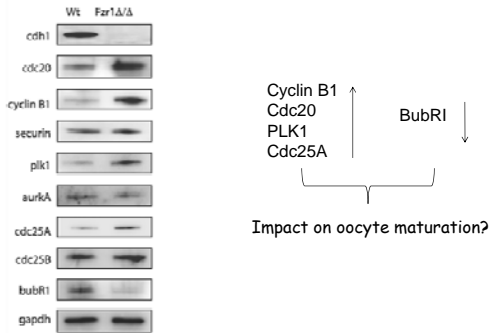
Nuclear targeted Cdh1 rescue can reduce cyclin B1 levels



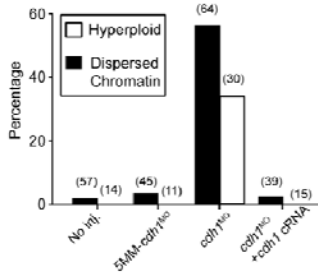
Message of talk

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Cdh1 loss changes levels of many proteins during GV arrest, not just Cyclin B1

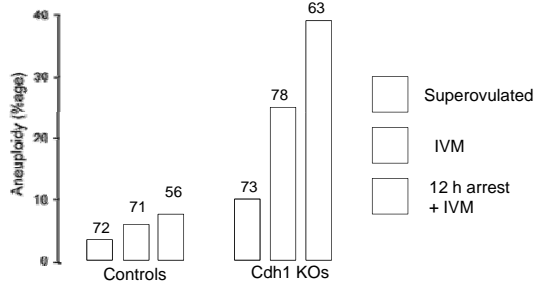


Cdh1 Knockdown leads to aneuploidy

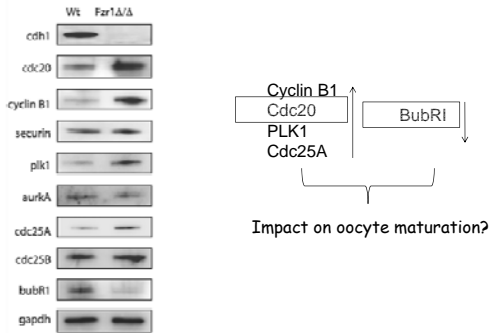


Reis et al (2007) Nature Cell Biology

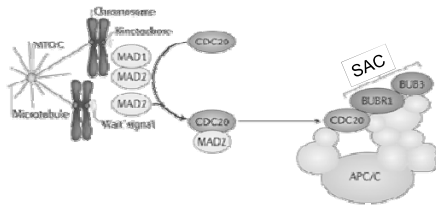
Are Cdh1 KO oocytes aneuploid?



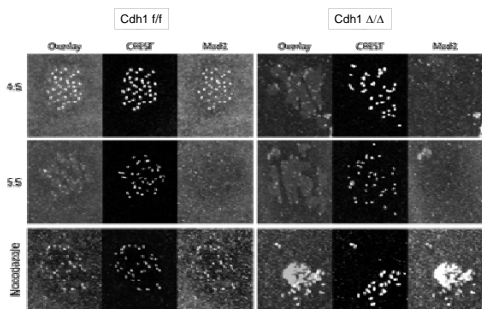
Cdh1 loss changes levels of many proteins during GV arrest, not just Cyclin B1



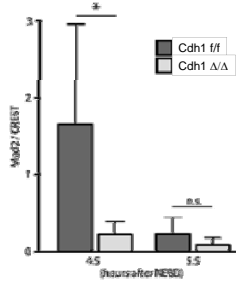
Spindle Assembly Checkpoint (SAC) inhibits APC^{Cdc20} : prevents aneuploidy



SAC switched off precociously following Cdh1 knockout



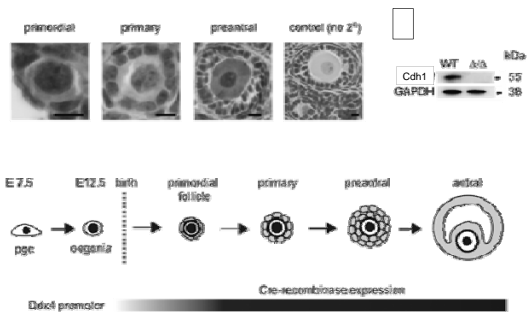
Kinetochores Mad2 is Cdh1 dependent



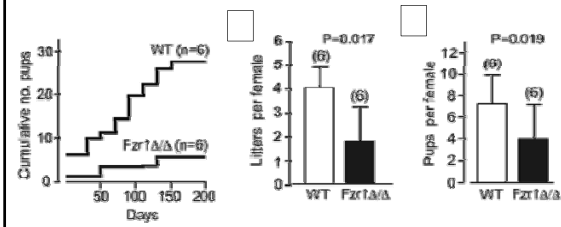
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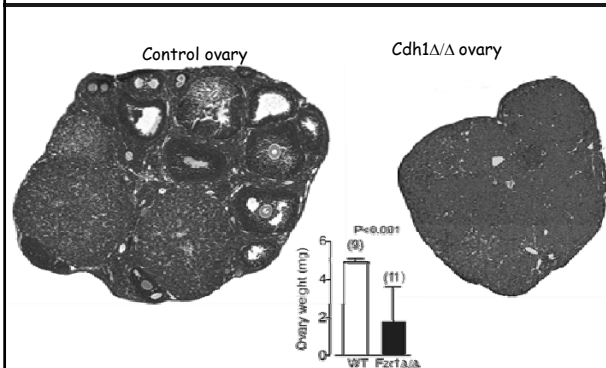
Cdh1 present in all stages of follicle growth



Early adult infertility in Ddx4-Cre Cdh1 knockout mice

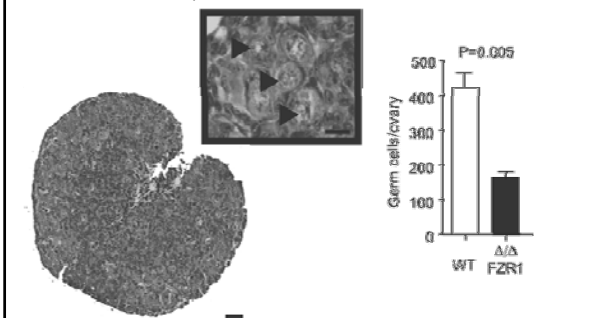


Premature ovarian failure in Cdh1 knockout mice



Cdh1 is needed for ovarian follicular endowment

Postnatal 1-2 days



Why is Cdh1 needed for follicular endowment?

APC^{Cdh1} → 'X' degradation → Meiotic prophase I arrest

'X' = cyclin B1?

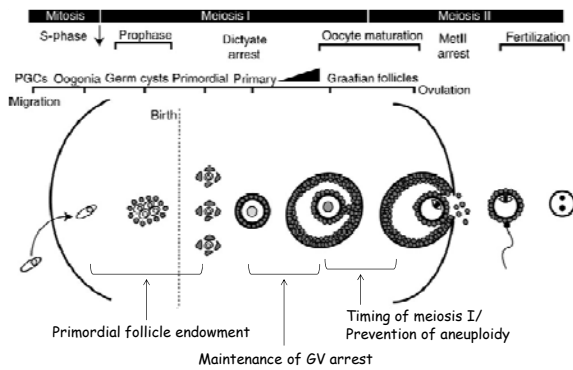
S → G2 → M S → G2 arrest

Cyclin B1 ↓

Cyclin B3 ↑

ATM/ATR ↑

Summary



Acknowledgements

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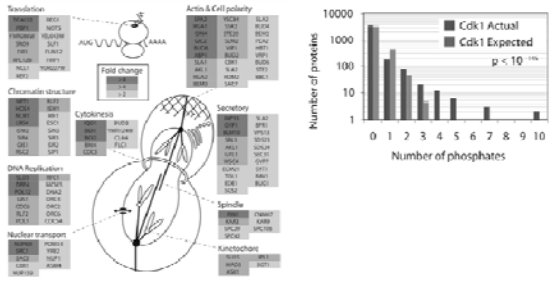
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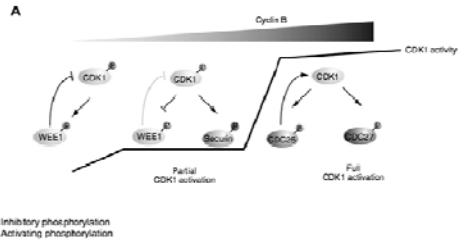


308 Cdk1 substrates identified in budding yeast



Holt et al (2009) Science

The G2 rise in Cyclin B1 drives mitosis entry



Deibler & Kirschner (2010) Mol Cell
