Polyploid Cell Cycles in Development, Genome Instability, and Cancer

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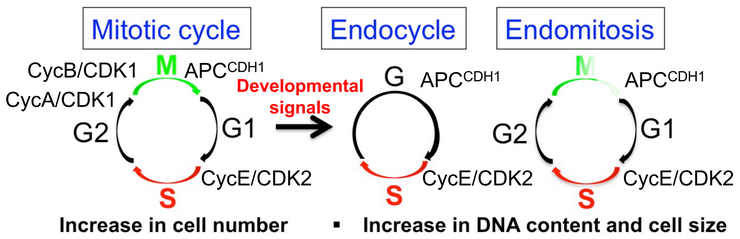
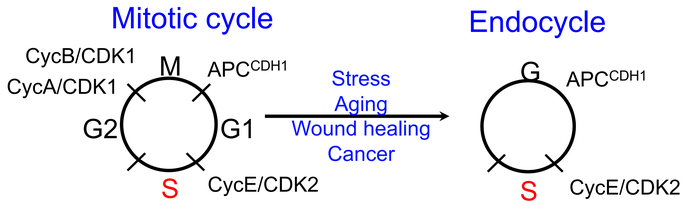
Fly Genetics at Indiana University
Powering the next 100 years of Drosophila research
http://www.bio.indiana.edu/~flyiu/

Endoreplication: a normal variant growth program in development



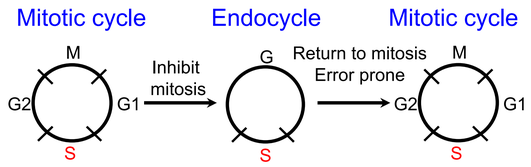
Developmental endoreplicating cells (**devECs**)

Cells also switch to endoreplication in response to conditional signals



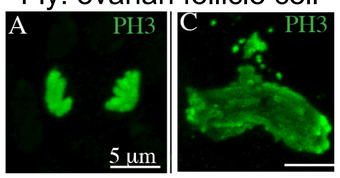
Induced endoreplicating cells (**iECs**)

iECs repress apoptosis and promote genome instability



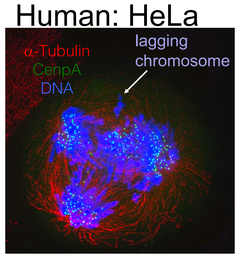
Experimental iEC
Fly: UAS - CycA^{RNAi} or UAS-Cdh1
Human cells: Cdk1 and Aurb kinase inhibitors

Fly: ovarian follicle cell



control iEC

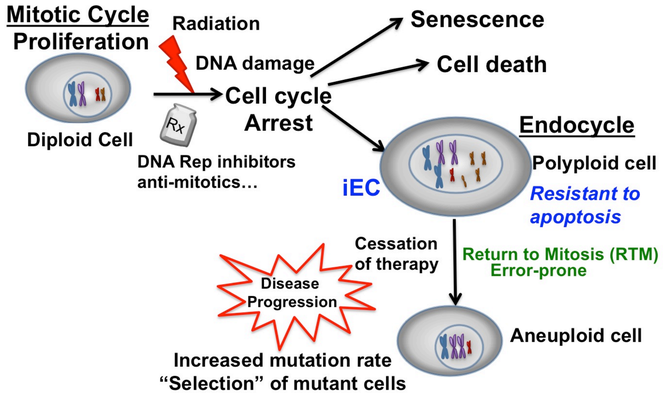
Human: HeLa



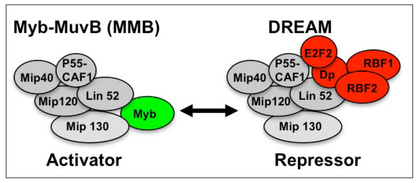
iEC

Transient endocycles: iEC return to mitosis (RTM) promotes genome instability in flies and humans

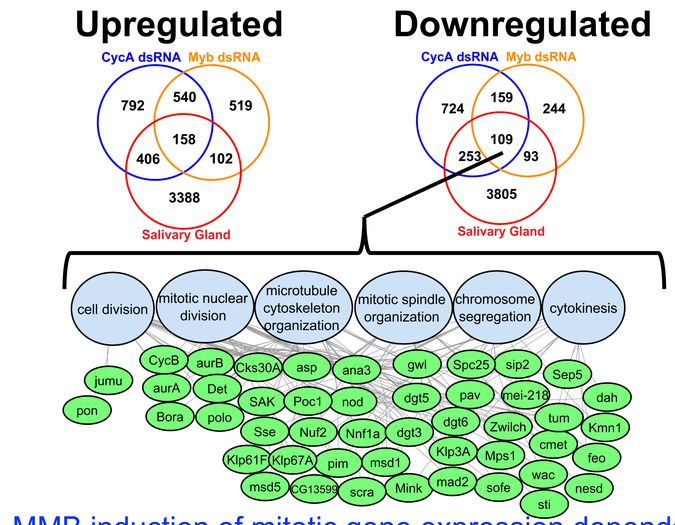
Model: Transient endocycles contribute to cancer therapy resistance and disease progression



An integrated RNA-Seq transcriptomic and genetic analysis of endocycles: downregulation of CycA-Myb-AurB regulatory network



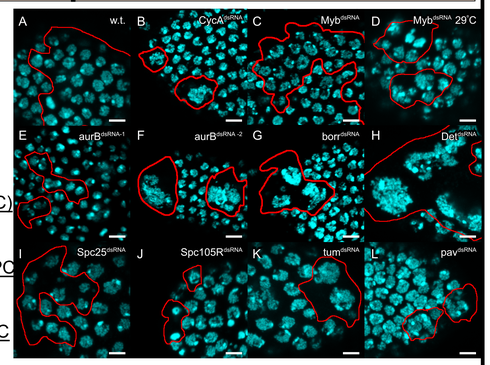
iECs and devECs have reduced expression of Myb target genes that function at multiple steps of mitosis and cytokinesis



MMB induction of mitotic gene expression depends on Cyclin A /CDK activity

Knockdown of different steps of a CycA-Myb-AurB network induce different types of endoreplication

Mitotic ovarian follicle cells
↓
FLP-On dsRNA in clones
3 days
↓
- # cells / clone
- Nuclear area
- DAPI intensity



Chromosome Passenger Complex (CPC)
AurB, Borr, Det

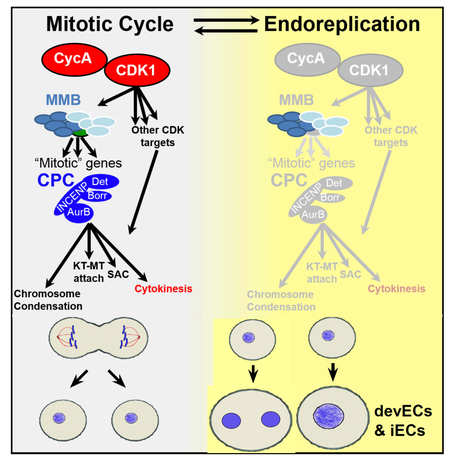
Kinetochore Proteins downstream of CPC
Spc25, Spc105R

Cytokinesis proteins downstream of CPC
Tum, Pav

- Panel E: AurB$^{dsRNA-1}$ was a weak RNAi knockdown, and resulted mostly in binucleate cells, indicating that chromosomes segregated by cytokinesis was repressed.
- Panel F: AurB$^{dsRNA-2}$ was a strong RNAi knockdown, and resulted in mostly mononucleate cells, indicating that both chromosome segregation and cytokinesis was repressed.
- Panel I, J: Knockdown kinetochore proteins resulted in cell death, not endorep.

Model and Summary

- ❖ devEC and iEC repress apoptosis
- ❖ Fly and human iEC return to mitosis with high levels of CIN
- ❖ Repression of a CycA - MMB –AurB pathway promotes endoreplication
- ❖ Repression of different steps of the pathway may explain the natural variation in polyploid cycles
- ❖ Endocycles may be a "normal" cell cycle that contributes to genome instability and cancer



Please contact us if you have questions!
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