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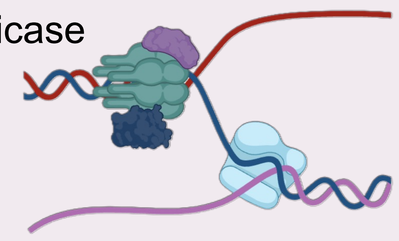
Parallels between the mechanisms by which CMG mutations block *C. elegans* cell fate divergence and cause human NK cell deficiency

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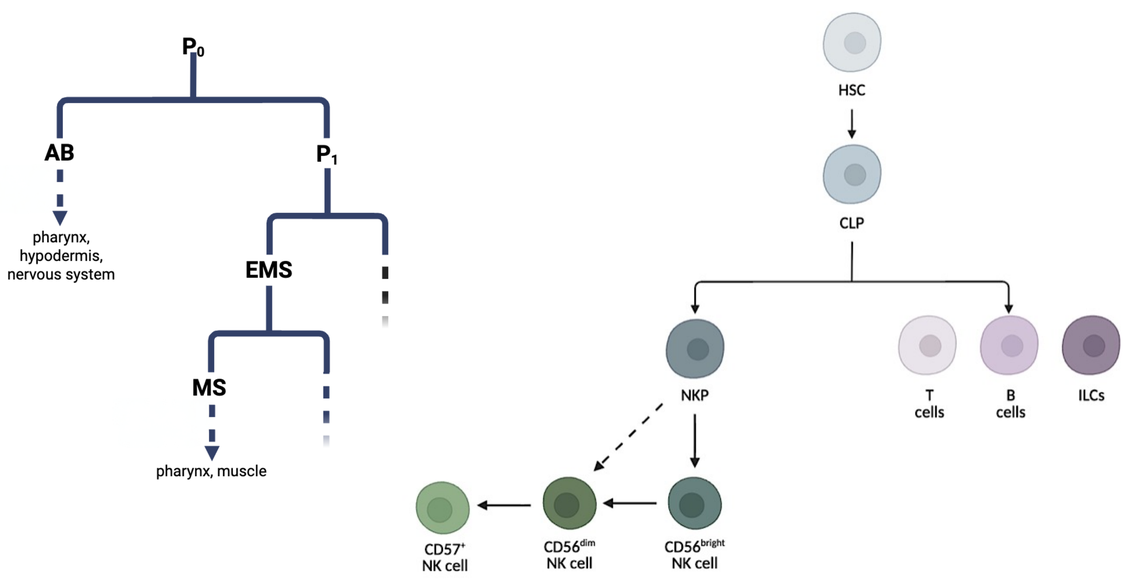
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Aim: Explore the extent to which the epigenetic mechanism by which CMG-mediated blocks in *C. elegans* cell fate divergence may apply to CMG-mediated human NKD

Background



- The CMG (Cdc45–MCM–GINS) helicase is classically responsible for unwinding DNA at the replication fork during cell division.
- Beyond this, CMG also plays a role in epigenetic inheritance: how histones and their modifications are passed on during replication.
- Mutations in CMG are linked to:
    - Block in cell death fate in *C. elegans*
    - Natural Killer cell deficiency (NKD) in humans
- Emerging evidence on *C. elegans* and mice embryonic stem cells (ESCs) suggest an epigenetic mechanism.
- Both phenotypes arise from disruptions in lineage specification, indicating a potentially shared mechanism.



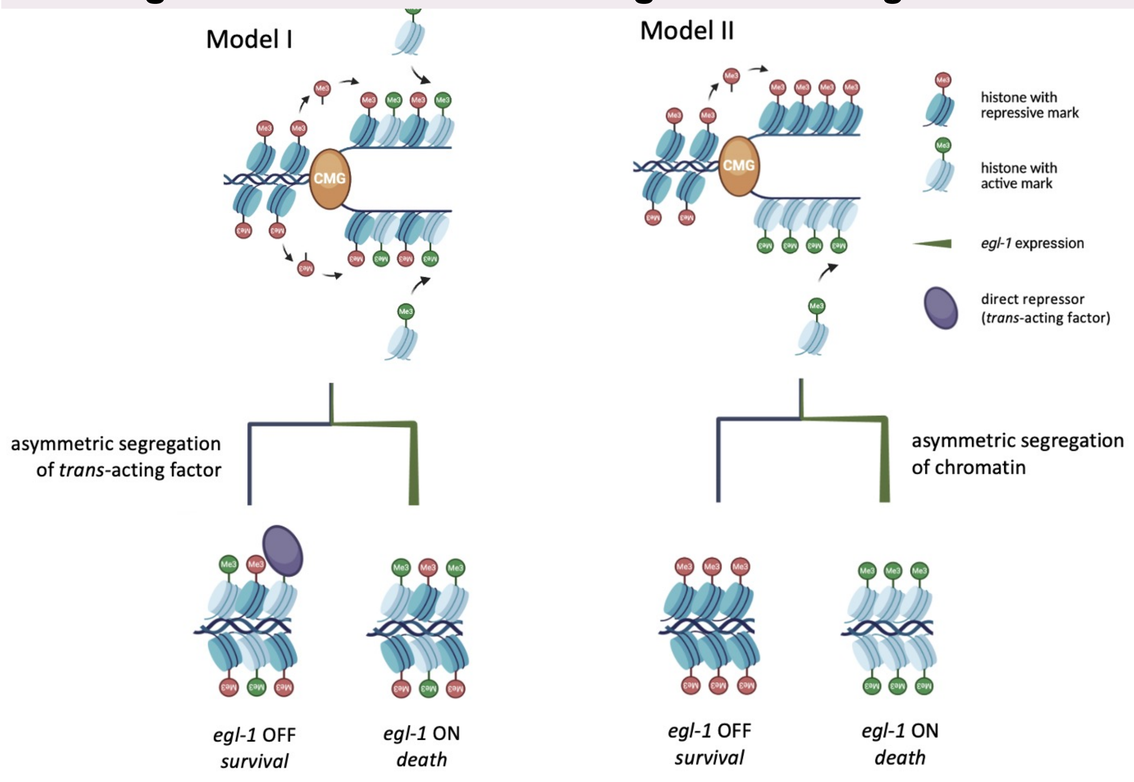
CMG-mediated block of *C. elegans* cell fate divergence

- Cell fate divergence depends on activation of pro-apoptotic gene *egl-1.*
- *egl-1* is a bivalent gene that can be rapidly switched ON/OFF after asymmetric cell division.
- CMG helicase acts as histone chaperone, enabling faithful inheritance of epigenetic marks required for *egl-1* activation.
- Working model: CMG loss-of-function disrupts histone inheritance → failure to upregulate *egl-1* in daughter fated to die.
- This is separate from CMG's classic role in DNA replication

CMG-mediated human NK cell deficiency

- NKD = genetic immune disease caused by monogenic variants leading to reduced NK cell number, maturation, and cytotoxicity.
- Relevant CMG mutations are primarily linked to replication stress, with the idea that NK cells are uniquely sensitive compared to other immune cells.
- This does not fully explain the phenotype

Working model for cell fate divergence in *C. elegans*



An epigenetics-based mechanism underlies both blocked cell fate divergence in *C. elegans* and NKD in humans

- Evidence from GINS-mediated NKD patients suggest a role beyond replication:
    - patient fibroblasts show only mild DNA damage without clear replication stress
    - neutropenia observed in these patients suggests disruption at the level of early HSC differentiation, not just NK proliferation
- In mouse ESCs, independent disruption of histone interactions (Mcm2-2A) leads to:
    - asymmetric histone inheritance
    - unequal distribution of epigenetic marks
    - impaired differentiation
- HSC differentiation is also regulated by bivalent genes. Disruption of epigenetic marks at these genes have been shown to prevent cell specification in other lineages.
- This supports an epigenetic model for both CMG-mediated cell death fate blocks and NKD

Conclusion

- CMG has dual roles in DNA replication and epigenetic regulation.
- This is separable in CMG-mediated blocks in *C. elegans* cell fate decisions. while separable in *C. elegans*, both likely contribute to NKD.
- Evidence suggests CMG dysfunction affects lineage specification via epigenetic mechanisms: impaired histone inheritance affects regulation of bivalent genes involved in differentiation.

Future work should:

- separate replication vs histone inheritance functions using Mcm2-2A mutants in *C. elegans.*
- Identify bivalent genes and pathways in NK cell specification
- Explore CMG activity within these two conditions in the context of other replisome factors, primarily MCM10, Pol ε, Pol α.

Main References:

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