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When the Family Treasure Is a Doormat

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Germ cells carry genetic information to the next generation, necessitating special attention to their genome maintenance. Two new studies in this issue of *Developmental Cell* (Bhargava et al., 2020; Dokshin et al., 2020) reveal an essential function of germ cell-specific protein GCNA in the genome maintenance of germ cells.

Germ cells are unique in their ability to carry genetic information from one generation to the next, making faithful maintenance of their genome particularly important. However, we do not have a good understanding of what supports the unique characteristics that enable long-term (transgenerational) maintenance of genome stability. While the germ cell genome can be considered a family treasure to be passed down the line, it is not tucked away for safety. Instead, germ cell genomes undergo the harshest abuses: DNA double-strand breaks (DSBs) for meiotic recombination by endogenous endonuclease Spo11, epigenetic overhaul to prepare for the next generation, and DNA hyper-condensation of the male germline accompanied by histone-to-protamine exchange. Therefore, the most precious genome of all is the one that is at the highest risk of damage and insult—as if your family treasure is treated like a doormat.

How do we protect our "heavily used heirloom"? Two new studies in this issue of *Developmental Cell*, one by Bhargava et al. (2020) and one from Dokshin et al. (2020), provide comprehensive characterization of the role of GCNA (germ cell nuclear antigen, or germ cell nuclear acidic peptidase) in diverse organisms (*C. elegans*, *Drosophila*, zebrafish, mouse, and human), shedding light onto the mechanism by which germline genome may be protected.

GCNA is a recently discovered protein that is highly enriched in germ cells and conserved throughout the Eukaryote domain, including unicellular eukaryotes such as *S. pombe* and *Chlamydomonas*, suggesting that GCNA's function is ancient (Carmell et al., 2016). Previous work noted that GCNA shows homology with a family of intrinsically disordered region (IDR)-containing metalloproteases, including Spartan and Wss1 (Carmell et al., 2016). Spartan family proteases are implicated in DNA repair, specifically by removing proteins from DNA-protein crosslinks (DPCs), which can interfere with transcription, replication, and DNA repair (Stingele et al., 2017).

Expanding on this notion, two new studies in this issue of *Developmental Cell* provide evidence that GCNA has a function similar to that of Spartan family proteases to specifically maintain germline genome (Bhargava et al., 2020; Dokshin et al., 2020). Consistent with its function in DNA repair and genome maintenance in the germline, *gcna* mutants exhibit genomic instability in germline, leading to reduced fertility. In the case of *C. elegans*, *gcna* mutants exhibit a gradual transgenerational loss in fecundity, a phenotype called "mortal germline." *C. elegans gcna* mutants exhibit a considerably elevated rate of mutations, and whole-genome sequencing revealed deletions, inversions, and complex rearrangements in *gcna* mutants (Dokshin et al., 2020). GCNA and Spartan appear to have overlapping roles, as double mutants show enhanced phenotypes in both *C. elegans* and *Drosophila* (Bhargava et al., 2020; Dokshin et al., 2020). Their functional divergence appears to be two-fold. First, GCNA functions specifically in germline, whereas Spartan functions to maintain genome integrity both in somatic cells and in the germline. Second, GCNA and Spartan appear to have different cell-cycle requirements: GCNA functions mainly in G2/M, whereas Spartan functions mainly in S phase, although GCNA's interaction with DNA replication proteins and *gcna* mutants' sensitivity to HU suggest their role in S phase as well.

Consistent with a potential role for GCNA in DPC removal, DPCs are increased in *Drosophila* and zebrafish *gcna* mutant embryos (Bhargava et al., 2020). Interestingly, a major protein found in DPCs in *gcna* mutants is Topoisomerase 2 (Top2), and Top2 and GCNA physically interact with each other (Bhargava et al., 2020; Dokshin et al., 2020). Topoisomerases are particularly susceptible to DPC formation because their enzymatic reaction involves covalent DNA-protein crosslink as a reaction intermediate. Further confirming a close relationship between GCNA and Top2, *gcna* mutants were found to be particularly sensitive to Top2 inhibitor (Dokshin et al., 2020; Borgermann et al., 2019). These results suggest a model wherein GCNA functions to maintain genome stability by removing Top2 from DPCs. In agreement with this model, fly, worm, and fish *gcna* mutants exhibit chromosome segregation defects that are consistent with defective Top2 function (Bhargava et al., 2020; Dokshin et al., 2020).

Although these data support the model in which GCNA's protease activity is the key in removing proteins (Top2) from DPCs, mouse GCNA's structure gives a twist to the story. Mouse GCNA has lost its protease domain (together with other likely functional domains such as the zinc finger and HMG box domains) and is almost entirely made up of an IDR. Yet the core functions and mechanisms of action are likely conserved, as the mouse *gcna* mutant is sterile with increased DNA damage, and mouse GCNA interacts with Top2 (Dokshin et al., 2020). A *C. elegans gcna* mutant that only retains the IDR region exhibited normal fecundity,

suggesting that the protease domain, zinc finger, and HMG box domains are indeed dispensable for GCNA function, although later generations of IDR-only mutants appear to exhibit genome-instability phenotypes (Bhargava et al., 2020). Yet a protease-dead *gcna Drosophila* mutant exhibits compromised functionality, although it can rescue maternal-effect embryonic lethality. It is possible that IDR can partner with another protein(s), possibly a protease, that helps remove DPCs (Bhargava et al., 2020).

Why does the germ cell genome require GCNA for its maintenance? In other words, what aspect of the germline genome makes it at higher risk of Top2-DPC formation? It is known that Top2 has germline-specific functions, such as chromosome separation of recombined chromosomes, histone-to-protamine exchange, and sperm chromatin condensation. However, GCNA is also expressed (and likely is required) before meiosis (Carmell et al., 2016). Based on GCNA's interaction with components of homologous recombination pathway (e.g., Mre11 and Rad50), Dokshin et al. (2020) propose that the germline genome may preferentially use the homologous recombination pathway to avoid mutations, and GCNA may be specialized in linking DPC repair to homologous recombination pathway, whereas somatic cells can rely on non-homologous end joining pathway for DNA repair.

The finding that GCNA is involved in DPC repair to maintain the germline genome significantly adds to our understanding of germ cell biology. Yet we cannot help but wonder why life ended up having such complicated ways to pass the genome to the next generation by making the germline's genome difficult to faithfully maintain, requiring extra help from GCNA.

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Casein Kinase 1δ Triggers Giant Ankyrin Expression

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During development, neurons form growth cones and neurites, but later reduce these activities to maintain a stable architecture. In this issue of *Developmental Cell*, LaBella et al. demonstrate that CK1δ plays a key role in winding down developmental processes exclusively by regulating poly(A) site choice to promote giant Ankyrin isoform expression.

During development, neurons sprout new dendrites and axons tipped with growth cones. Once these neurite projections have reached their targets, synapses are formed, and neurons switch from outgrowth to maintenance of the established architecture, subject to refinement and remodeling. We lack a comprehensive understanding of what mechanisms prevent neurons from continuing to sprout new growth cones at later stages. In this issue of *Developmental Cell*, LaBella et al. (2020) demonstrate that Casein kinase 1δ (CK1δ) is important for blocking new growth cone formation in older neurons, primarily by regulating alternative poly(A) site selection in order to facilitate expression of the giant isoform of Ankyrin.

In this study, the authors examine the role of CK1δ in the development and maintenance of the GABAergic dorsal D (DD) and ventral D (VD) neurons in *C. elegans*. The cell bodies of these neurons, located in the ventral nerve cord (VNC), extend neurites within the VNC and dorsal nerve cord (DNC) that are connected by a commissural projection. In general, early development seems normal in CK1δ mutants: in the late first larval (L1) stage, when only DD neurons are present, a fraction of DD neurites of CK1δ mutants form interstitial growth cones in the commissures, which occasionally perturb the stability of any already existing DNC neurites, but the majority are normal. Additionally, growth cones of the later-developing VD neurons initially form normal commissural projections in CK1δ mutants, and later VNC synaptogenesis appears normal in the late second larval (L2) stage. However, by the young adult stage, when wild-type DD and VD neurons have long ago established a stable overall architecture, CK1δ mutant neurons accumulate growth defects. Along the commissures, animals lacking CK1δ progressively amass ectopic growth cones, ectopic neurite branches, and