RESEARCH ARTICLE

DEVELOPMENTAL BIOLOGY

# Vertebrate diapause preserves organisms long term through Polycomb complex members

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Diapause is a state of suspended development that helps organisms survive extreme environments. How diapause protects living organisms is largely unknown. Using the African turquoise killifish (*Nothobranchius furzeri*), we show that diapause preserves complex organisms for extremely long periods of time without trade-offs for subsequent adult growth, fertility, and life span. Transcriptome analyses indicate that diapause is an active state, with dynamic regulation of metabolism and organ development genes. The most up-regulated genes in diapause include Polycomb complex members. The chromatin mark regulated by Polycomb, H3K27me3, is maintained at key developmental genes in diapause, and the Polycomb member CBX7 mediates repression of metabolism and muscle genes in diapause. CBX7 is functionally required for muscle preservation and diapause maintenance. Thus, vertebrate diapause is a state of suspended life that is actively maintained by specific chromatin regulators, and this has implications for long-term organism preservation.

To survive extreme conditions, many species have evolved specific states of suspended life in the form of hibernation, torpor, and diapause. Diapause suspends embryonic development when environmental conditions are harsh, enabling birth in favorable conditions. The African turquoise killifish (*Nothobranchius furzeri*) has been proposed as a vertebrate model to study embryonic diapause (*1*, *2*). This killifish lives in transient ponds that are only present during the rainy season and entirely desiccate during the dry season (*3*–*6*). To survive the long drought and enable perpetuation of the species, African killifish embryos enter diapause (*1*, *2*) (Fig. 1A). Although features of diapause have been described in killifish species (*6*, *7*), the mechanisms by which diapause protects organisms remain unknown.

### Diapause protects complex organs with no trade-offs for future life

We characterized African killifish diapause and investigated whether diapause comes with trade-offs for subsequent life. More than 70% of African killifish embryos enter diapause and they stay in this state for 5 to 6 months before naturally exiting (Fig. 1B and fig. S1). Some embryos remain in diapause for >10 months and occasionally 2 years (Fig. 1B, inset, and table S1). Hence, diapause is longer than the adult life of African killifish and may reflect a programmed adaptation to survive the annual drought while also protecting against unpredictable weather. Diapause embryos have muscles, a heart, primordial germ cells, a brain comprising stem and differentiated cells, as well as complex systems such as neuromuscular junctions (Fig. 1, C and D, and fig. S2). Staying in diapause for 5 months (a period equivalent to their adult life span) did not negatively affect subsequent adult growth, fertility, or subsequent life span of these killifish (Fig. 2, A to C, and fig. S3). Thus, the time spent in diapause does not come with observed trade-offs for future life, and diapause confers protective mechanisms to complex organs against damage caused by the passage of time.

### Diapause is an active state with dynamic gene regulation

To understand how diapause preserves a complex organism, we first performed a transcriptomic time course in diapause. Using the change in heartbeat pattern as an early diapause hallmark, we collected synchronized populations of killifish embryos for RNA sequencing (RNA-seq): embryos in diapause for 3 days, 6 days, and 1 month, and embryos in development right before and after the time corresponding to diapause onset (Fig. 3A, figs. S4 and S5A, and table S2). Diapause time points were easily separated by principal component analysis and clustering (Fig. 3B, fig. S5B, and table S3). The transcriptome was substantially reprogrammed in diapause: >33% of the transcripts changed more than twofold in diapause (fig. S5C) and had dynamic expression patterns (fig. S5D). Genes involved in cell proliferation and organ development were down-regulated throughout or late in diapause, respectively (Fig. 3C and fig. S5E). One notable exception was muscle. Genes implicated in muscle development and function were up-regulated early and down-regulated late in diapause (Fig. 3D and table S4), suggesting that muscle might be maintained in a different manner in diapause. Finally, genes involved in autophagy and metabolic pathways (e.g., nucleotides and amino acids) were up-regulated throughout diapause (Fig. 3D, fig. S5E, and table S4). Thus, diapause is an active state, with up-regulation of metabolic genes and dynamic regulation of organ development genes.

### Switch to specific Polycomb complex members in diapause

To identify candidate regulators of organ maintenance in diapause, we focused on the most up-regulated genes in diapause. Although several of them relate to amino acid metabolism, three of the 10 most up-regulated genes are implicated in chromatin regulation: *EZH1*, *CBX7(1of2)* (hereafter *CBX7*), and *PCGF5* (Fig. 3E and table S4). EZH1 is a core Polycomb complex enzyme that trimethylates lysine 27 in histone H3 (H3K27me3), whereas CBX7 binds to H3K27me3 and mediates specific transcriptional repression (*8*–*12*) (Fig. 4A). Overall, diapause was accompanied by a switch to members of the canonical Polycomb repressive complex 1 (PRC1) (Fig. 3F and fig. S6), suggesting that a specialized Polycomb complex may be important for the diapause state.

### H3K27me3, a mark regulated by Polycomb complex members, is maintained at key organ genes in diapause

Polycomb complex members are critical for stem cell identity, development, and cancer, and they act by depositing or binding to histone marks, notably H3K27me3 (*10*–*12*) (Fig. 4A). We first assessed the global H3K27me3 landscape in diapause by performing H3K27me3 chromatin immunoprecipitation sequencing (ChIP-seq) in diapause or developing (without diapause) embryos (fig. S7). Despite the substantial transcriptomic changes in diapause, the H3K27me3 landscape was very similar in diapause compared with development (Fig. 4B). Genes with maintained H3K27me3 (~7000 genes) were mostly involved in organ development, whereas genes that were not marked (~14,000 genes) were involved in cellular processes (e.g., autophagy) (Fig. 4B and fig. S7G), suggesting maintenance of developmental identity in diapause. Overall, H3K27me3 did not correlate with gene repression in diapause (fig. S7D). However, genes with maintained H3K27me3 (e.g., organ

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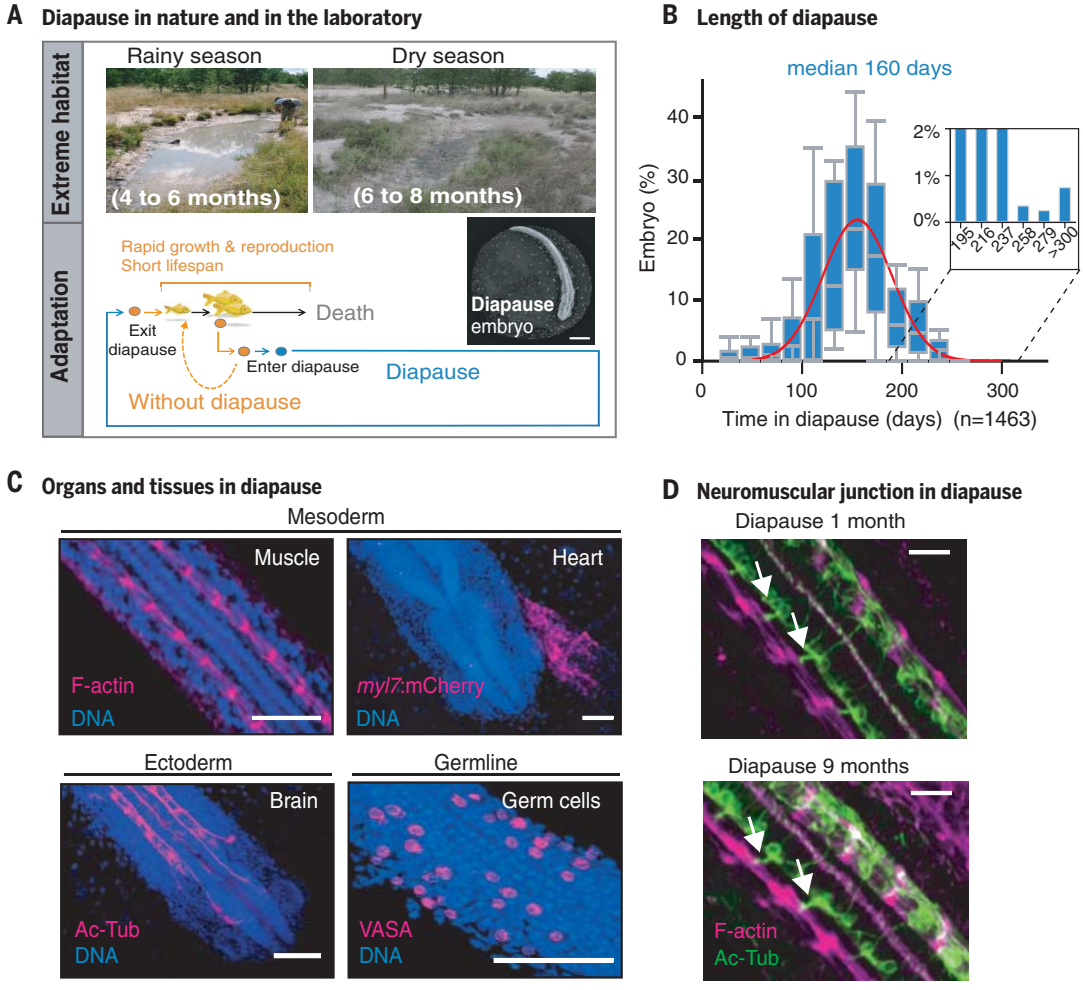



**Fig. 1. Diapause lasts for long periods of time and diapause embryos have complex organs.** (**A**) African killifish life cycle. [Natural habitat images: copyright 2015 from *The Evolutionary Ecology of African Annual Fishes* by M. Reichard.] Scale bar in embryo image, 200 μm. (**B**) Percentage of embryos that stayed in diapause for the indicated length of time (1463 embryos). Boxes show the median and interquartile ranges. Whiskers indicate maximum 1.5 interquartile range. Red indicates the Gaussian curve fitted to the distribution. About 1% of embryos stayed in diapause for >300 days (inset) (table S1). (**C** and **D**) Killifish embryos in diapause have muscle, heart, brain, germ cells, and neuromuscular junctions. Muscle: Alexa Fluor-647–labeled phalloidin. Heart: Transgenic line expressing cardiac-specific mCherry. Brain: Antibodies to SOX2, GFAP, and acetylated tubulin (Ac-Tub). Germ cells: Antibodies to VASA. Scale bars, 50 μm. Arrows indicate neuromuscular junctions.

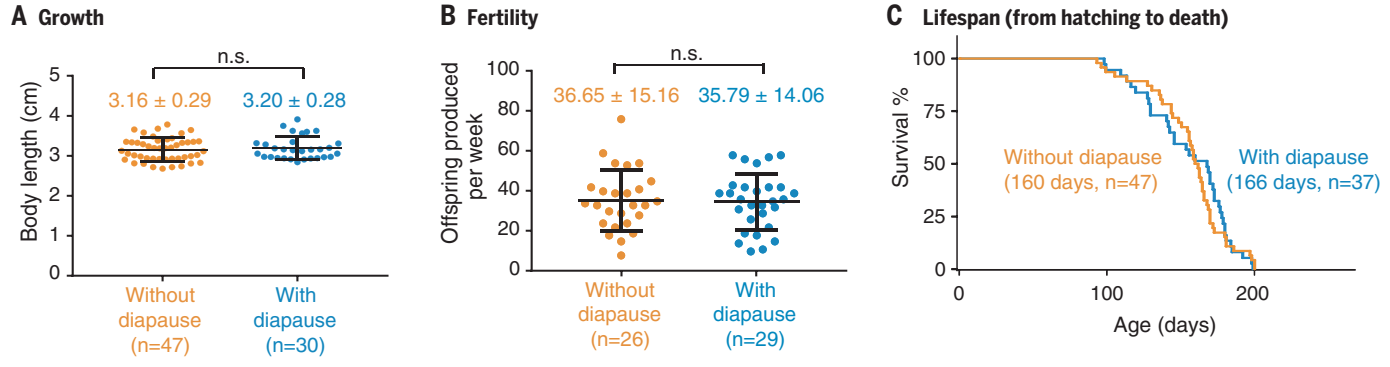
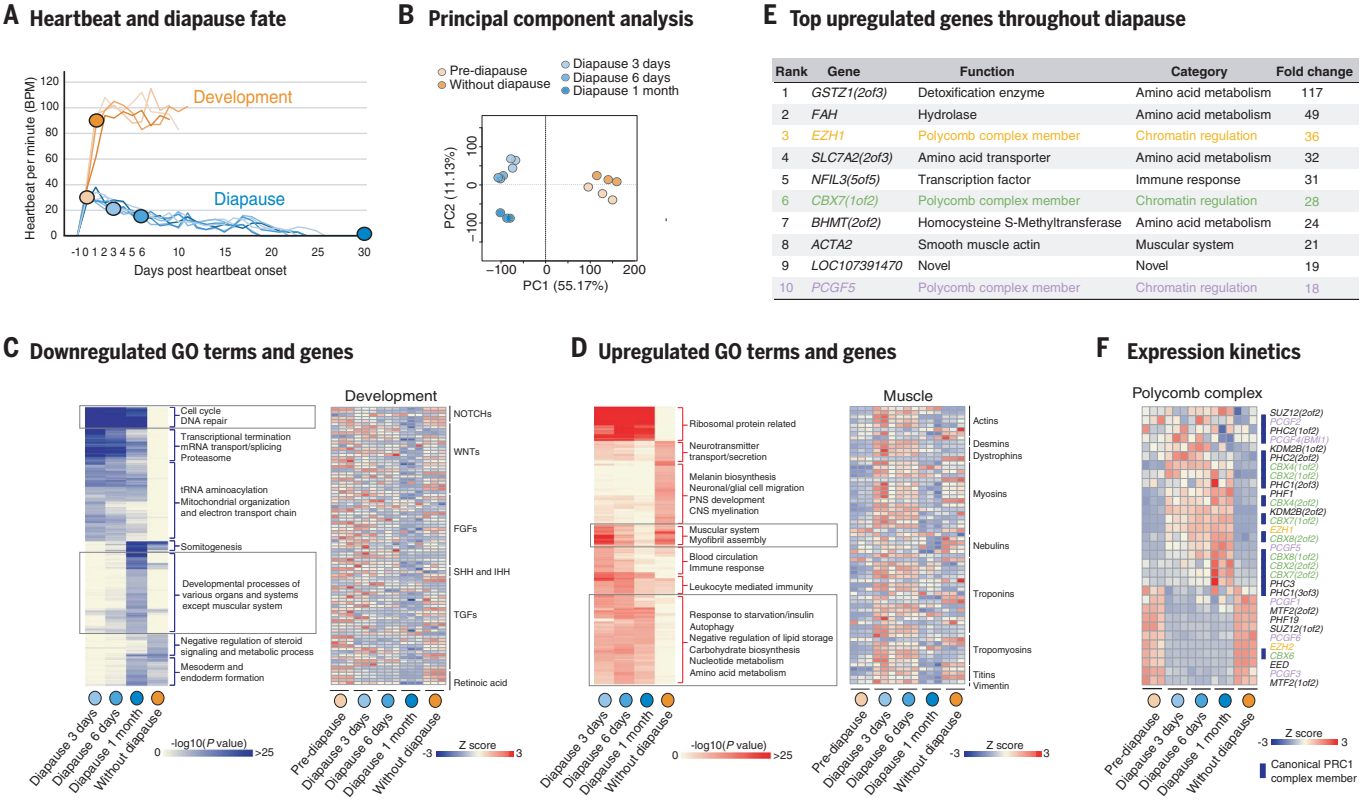



**Fig. 2. Diapause protects complex organisms with no trade-offs for future life.** (**A**) Mean ± SD of body length of adult male fish originating from 47 embryos that developed directly (without diapause; orange) or 30 embryos that stayed in diapause for 5 months (with diapause; blue). Each dot represents an individual fish. $P = 0.73$, Mann–Whitney unpaired nonparametric test. n.s., nonsignificant (see table S1). (**B**) Mean ± SD of offspring number from 3 breeding pairs originating from embryos without diapause (orange) or in diapause for 5 months (blue). Each dot represents a weekly collection of offspring. $P = 0.95$, Mann–Whitney unpaired nonparametric test (table S1). (**C**) Kaplan–Meier survival curves of 47 adults originating from embryos without diapause (one censored) and 37 adults from embryos that stayed 5 months in diapause. Log-rank (Mantel–Cox) test, $P = 0.84$. Median life spans are shown in parentheses (table S1).

development genes, including muscle genes) tended to be down-regulated late in diapause (Fig. 4, C and D; fig. S7, E and F; and table S5), and a few genes with H3K27me3 loss were up-regulated in diapause (e.g., *CDKN1B*) (fig. S7, H and I). Thus, the switch to specific Polycomb complex members may serve to maintain H3K27me3 at genes involved in organ development and may mediate their repression late in diapause.

**Polycomb complex member CBX7 mediates repression of lipid metabolism and muscle genes**

Because H3K27me3 is maintained in diapause, we next investigated whether Polycomb members that act downstream of H3K27me3 could




| Rank | Gene | Function | Category | Fold change |
|---|---|---|---|---|
| 1 | *GSTZ1(2of3)* | Detoxification enzyme | Amino acid metabolism | 117 |
| 2 | *FAH* | Hydrolase | Amino acid metabolism | 49 |
| 3 | *EZH1* | Polycomb complex member | Chromatin regulation | 36 |
| 4 | *SLC7A2(2of3)* | Amino acid transporter | Amino acid metabolism | 32 |
| 5 | *NFIL3(5of5)* | Transcription factor | Immune response | 31 |
| 6 | *CBX7(1of2)* | Polycomb complex member | Chromatin regulation | 28 |
| 7 | *BHMT(2of2)* | Homocysteine S-Methyltransferase | Amino acid metabolism | 24 |
| 8 | *ACTA2* | Smooth muscle actin | Muscular system | 21 |
| 9 | *LOC107391470* | Novel | Novel | 19 |
| 10 | *PCGF5* | Polycomb complex member | Chromatin regulation | 18 |

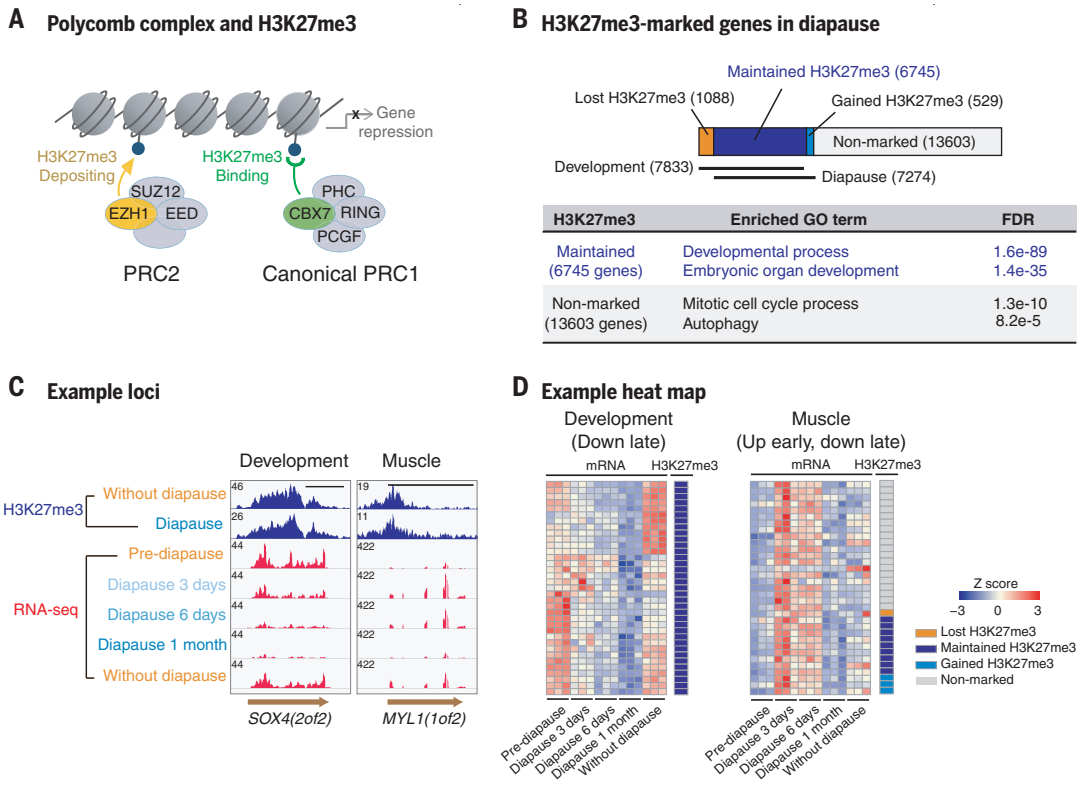
**Fig. 3. Dynamic gene regulation in diapause and switch to specific Polycomb complex members.** (**A**) Heartbeat patterns of embryos developing without diapause (orange) or entering diapause (blue) (see also fig. S4, A and B). Each colored circle represents a time point for RNA-seq selected on the basis of heartbeat onset and pattern. (**B**) Principal component analysis on log2-transformed transcripts per million (TPM) of all genes. Each dot represents the transcriptome from pooled embryos. (**C** and **D**) Left: Heat map of gene ontology (GO) terms enriched by differentially expressed genes with false discovery rate (FDR) < 0.01 in at least one of the time points (table S4 and data S1). Enriched GO terms are clustered based on *P* values (blue, down-regulated; red, up-regulated). Right: Heat maps of key gene families of development or muscle. *Z*-scores are based on the normalized expression value of each gene (TPM). (**E**) Genes most up-regulated in diapause (fold change > 2, FDR < 0.01, TPM > 25 in all 3 diapause conditions) but not during development (without diapause) (fold change < 2) (table S4). (**F**) Heat map showing the expression profile of select Polycomb complex members (see also fig. S6, A and B). *Z*-scores are based on the normalized expression value of each gene (TPM). Paralog numbers are shown in parentheses.

mediate the repression of specific genes. We focused on CBX7 because it binds H3K27me3 (*8*, *9*, *13*–*16*) and is highly up-regulated throughout diapause. Using CRISPR-Cas9 genome editing (*17*), we generated two independent *CBX7* killifish mutants predicted to give rise to premature stop codons (Fig. 5A and fig. S8). RNA-seq analysis of wild-type (WT) and *CBX7* mutant embryos in diapause revealed that up-regulated (i.e., derepressed) genes in *CBX7* mutant embryos were enriched for metabolism and cytokine and hormone regulation processes, whereas down-regulated genes were enriched for muscle and neurotransmission processes (Fig. 5B; fig. S9, A to C; and table S7). Of the derepressed genes in *CBX7* mutant embryos, 142 also exhibited H3K27me3 maintenance in diapause and could therefore represent direct targets of CBX7. These targets are implicated in lipid metabolism (e.g., *PLTP*) and organ development (e.g., *SOX9*), and one of them, *UBE2H*, is involved in muscle atrophy (*18*, *19*) (Fig. 5, C and D, and fig. S9, D and E). The other gene expression changes in *CBX7* mutants, down-regulation of muscle assembly genes (e.g., *NEBL*), could be indirect consequences or reflect phenotypic differences in *CBX7* mutants (Fig. 5, C and D, and fig. S9C). Thus, CBX7 could mediate the repressive effect of H3K27me3 on specific lipid metabolism and muscle genes.

### CBX7 is required for muscle preservation and diapause maintenance

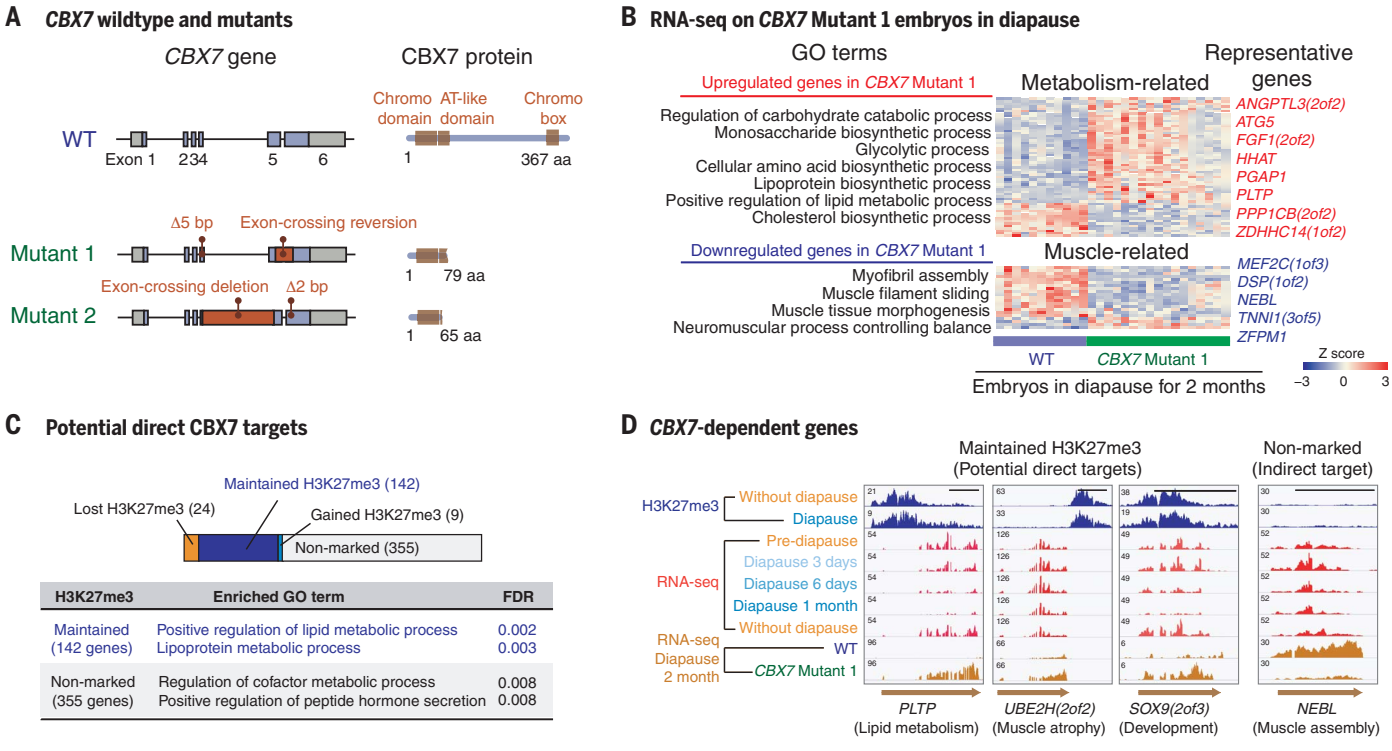
We next tested the functional importance of CBX7 in diapause. *CBX7* mutant embryos entered diapause normally and initially were similar to their WT counterparts. However, *CBX7* mutant embryos from both lines exhibited deterioration in their muscles after a month in diapause (Fig. 6, A and B). This is consistent with the up-regulation of the muscle atrophy gene *UBE2H* and the down-regulation of several muscle assembly genes in *CBX7* mutants. Muscle defects in *CBX7* mutant embryos were specific to diapause (Fig. 6, B and C), consistent with the selective expression of *CBX7* in diapause (fig. S6B). *CBX7* mutants did not exhibit overt defects in neurons or neuromuscular junctions (Fig. 6, D and E, and fig. S10, A and B). But these CBX7 mutants could not stay in the diapause state as long as their WT counterparts did, although they were viable afterward (Fig. 6F and fig. S10C). Thus, CBX7 is required for long-term preservation of muscles in diapause and for the maintenance of this state.

Our results show that killifish diapause preserves organs, complex systems such as neuromuscular junctions, and various cell types for long periods of time without trade-offs for future life. Diapause is an active and dynamic state, with genes involved in organ development being down-regulated late. We identify specific members of the Polycomb complex, notably CBX7, as functional regulators of long-term organ preservation in diapause. CBX7 may maintain muscles by directly and indirectly regulating specific genes involved in muscle function and metabolism (fig. S10D). It will be interesting to determine how *CBX7* deficiency in diapause affects subsequent adult life. The role of CBX7 and other specialized Polycomb




| H3K27me3 | Enriched GO term | FDR |
|---|---|---|
| Maintained (6745 genes) | Developmental process | 1.6e-89 |
| | Embryonic organ development | 1.4e-35 |
| Non-marked (13603 genes) | Mitotic cell cycle process | 1.3e-10 |
| | Autophagy | 8.2e-5 |

**Fig. 4. H3K27me3 is maintained at key organ genes in diapause.** (**A**) Selected members of the Polycomb complex and their interaction with H3K27me3. (**B**) Number of genes marked by H3K27me3 that are maintained, lost, or gained in diapause or not marked in either state. GO terms associated with maintained H3K27me3 or unmarked genes in embryos in diapause (table S6; see also fig. S7G). (**C**) Example loci with H3K27me3 ChIP-seq and RNA-seq peaks in development (without diapause) or diapause. The data range of H3K27me3 tracks was individually autoscaled. Scale bars, 5 kb. (**D**) Heat maps showing genes with dynamic transcriptomic trajectories in diapause and H3K27me3 marking. *Z*-scores are based on the normalized expression value of each gene (TPM).




| H3K27me3 | Enriched GO term | FDR |
|---|---|---|
| Maintained (142 genes) | Positive regulation of lipid metabolic process | 0.002 |
| | Lipoprotein metabolic process | 0.003 |
| Non-marked (355 genes) | Regulation of cofactor metabolic process | 0.008 |
| | Positive regulation of peptide hormone secretion | 0.008 |

**Fig. 5. The Polycomb complex member CBX7 mediates repression of a subset of lipid metabolism and muscle genes.** (**A**) Two independent *CBX7* mutant lines were generated by CRISPR-Cas9 genome editing. (**B**) GO terms (FDR < 0.01) enriched by differentially expressed genes (fold change > 1.5, FDR < 0.01) of *CBX7* Mutant 1 embryos in diapause for 2 months. Relevant genes were clustered into heat maps on the basis of expression level (TPMs) across 11 WT and 17 *CBX7* Mutant 1 embryos. Representative genes are shown on the right (red, up-regulated; blue, down-regulated; see also fig. S9C). (**C**) Number of genes up-regulated in *CBX7* Mutant 1 embryos and marked by H3K27me3 (potential direct targets) and their associated GO terms. (**D**) Example loci (as in Fig. 4C). Scale bars, 2 kb.

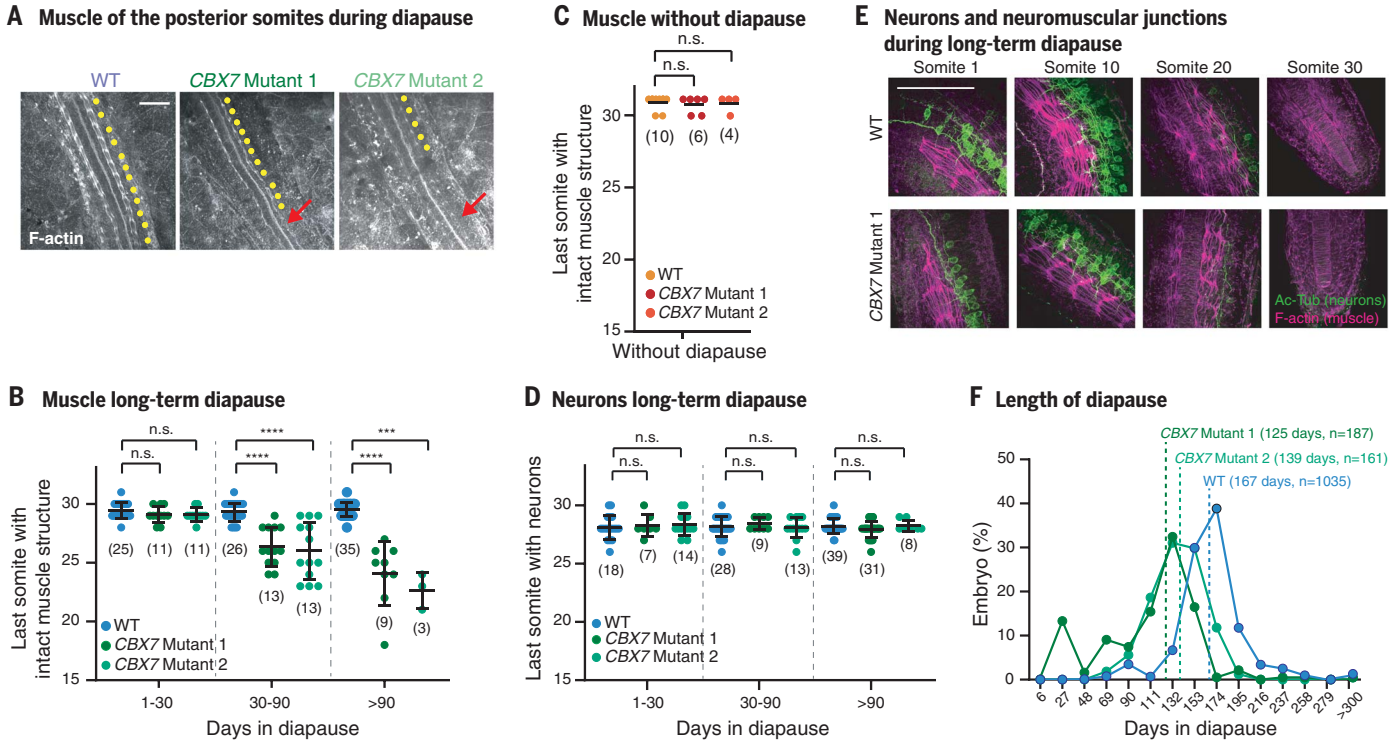



**Fig. 6. The Polycomb complex member CBX7 is required for muscle preservation and diapause maintenance.** (**A**) Example of muscle deterioration in *CBX7* mutant embryos in diapause for 5 months. Muscle: Alexa Fluor-647–labeled phalloidin. Red arrows: posterior somites lacking muscle fiber bundles. Yellow dots: somites with muscle fiber bundles. Scale bar, 50 μm. (**B** and **C**) Mean ± SD of the number of the last somite with intact muscle in WT and *CBX7* mutant embryos at different times in diapause (B) or without diapause (C). Each dot represents an embryo. Embryo numbers are shown in parentheses. ***$P < 0.001$, ****$P < 0.0001$, Mann–Whitney unpaired nonparametric test (table S1). (**D**) Mean ± SD of the number of the last somite with neurons in WT and *CBX7* mutant embryos in diapause [as in (B)]. (**E**) Neurons and neuromuscular junctions in the somites of WT and *CBX7* Mutant 1 embryos in diapause for 4 months. Muscle: Alexa Fluor-647–labeled phalloidin. Neurons: Antibodies to Ac-Tub (see also fig. S10A). Scale bar, 50 μm. (**F**) Percentage of WT *CBX7* mutant embryos that stayed in diapause for the indicated length of time. Median diapause length and embryo numbers are shown in parentheses.

complex members could extend to other organisms and forms of long-term preservation (*20*–*22*) or to longevity (*23*, *24*). Indeed, Polycomb complex genes are involved in insect diapause and seasonal responses in plants (*20*–*22*). Finally, because the metabolic pathways up-regulated during diapause in killifish are similar to those up-regulated in *Caenorhabditis elegans* Dauer (*25*), longevity mutants (*26*, *27*), and mammalian hibernation (*28*, *29*), a switch in metabolic and chromatin states could coordinate longevity and suspended life. Our study has important implications for long-term organism preservation and resistance to extreme environments.

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## SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/367/6480/870/suppl/DC1
Materials and Methods
Tables S1 to S8
Figs. S1 to S10
Data S1
References (*30*–*48*)

View/request a protocol for this paper from *Bio-protocol*.


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**Putting vertebrate development on hold**

Suspended animation is an often-used device in science fiction, but it also exists in several forms in nature: hibernation, torpor, and diapause. Hu *et al.* studied diapause in the African turquoise killifish, a vertebrate model system (see the Perspective by Van Gilst). They found that diapause protects a complex living organism without trade-offs for future growth, fertility, and even life span. Diapause is actively regulated, with a dynamic switch to specific Polycomb complex members. One Polycomb member, CBX7, is critical for the regulation of organ genes and is involved in muscle preservation and diapause maintenance. This work illuminates the mechanisms that underlie suspended life.

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