Warm and cold temperatures have distinct germline stem cell lineage effects during *Drosophila* oogenesis

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First decision letter

MS ID#: DEVELOP/2021/200149

MS TITLE: Warm and cold temperatures induce distinct germline stem cell lineage responses during Drosophila oogenesis

AUTHORS: Ana Caroline P Gandara and Daniela Drummond-Barbosa

I have now received all the referees' reports on the above manuscript, and have reached a decision. As you will see, the referees express interest in your work, but have some significant concerns and provide recommendations. One major concern in the work is the lack of direct evidence of mating rates in animals when raised at higher temperature, especially given that multiple studies in the field have directly measured these. A second equally significant concern is that the effect of lower temperature on reproduction seems to be simply slower development rather than an instructive mechanism. Experiments to address both of these concerns are thus important. In addition, Reviewer 1 suggests experiments to significantly improve the rigor of the analysis with TrpA1. These include conducting rescue experiments of TrpA1 single mutant and the synergistic effects of TrpA1 and Grb28b. These are excellent recommendations, and very much in line with the expected rigor of analysis for Development. Reviewer 2 points out an apparent contradiction in that the TrpA1(1) homozygous females had markedly improved oocyte quality compared to controls, which would need to be addressed.

If you are able to revise the manuscript along the lines suggested, I will be happy receive a revised version of the manuscript. Your revised paper will be re-reviewed by one or more of the original referees.

Please attend to all of the reviewers' comments and ensure that you clearly highlight all changes made in the revised manuscript. Please avoid using 'Tracked changes' in Word files as these are lost in PDF conversion. I should be grateful if you would also provide a point-by-point response detailing how you have dealt with the points raised by the reviewers in the 'Response to Reviewers' box. If you do not agree with any of their criticisms or suggestions please explain clearly why this is so.

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Reviewer 1

Advance summary and potential significance to field

This manuscript by Gandara and Drummond-Barbosa examines how raising females and males at sub optimally high (29 C) and low (18) temperatures impacts oocyte growth, development, and quality in Drosophila. Additionally, the authors identify a conserved warm sensitive sensor. While this work is important in light of a worldwide increase in temperatures due to global warming, the manuscript contains several significant issues that must be addressed before publication.

Comments for the author

Major Comments
1 The authors conclude that raising females at 29°C results in the death of vitellogenic follicles and lowers oocyte quality while raising males at 29°C impairs male fertility (Figure 7). However, it is well-established in the literature that high temperatures decrease mating success in Drosophila. The authors do not adequately address this confounding factor. Hatch rates and death of vitellogenic chambers are both impacted by mating and fertilization.
Observing the number of stage 14 oocytes is not an adequate substitute for directly examining laid eggs, for either the presence of sperm or an attempt at early embryogenesis. Therefore, the rigor of the manuscript would be improved if the authors determined what percentage of eggs were fertilized when males and females are raised at various temperatures. Subsequently, the authors should determine what component of the decrease in oocyte quality (as determined by hatch rates) or death of vitellogenic chambers is due to decreased mating.
2 The authors conclude that the temperature receptor TrpA1 is partially required for the decrease in oocyte quality observed at higher temperatures.
Specifically, they show that TrpA1 partially rescues the oocyte quality defects observed at higher temperatures. Unfortunately, the authors examined a single null allele of TrpA1. To make this conclusion, they need to rescue this phenotype, with a transgenic rescue construct or duplication, and/or generate a second allele of TrpA1 that has the same phenotype. Similarly, the double mutant analysis of TrpA1 with Grb28b, needs to be performed with additional alleles of TrpA1 and Grb28b or the synergistic phenotype needs to be rescued with a transgenic rescue construct or duplication.

Minor Comments
1 Page 7 figure 4. It is not clear if the authors are concluding females raised at 18 degrees have increased number of 16 cell cysts relative to wild type due to decreased apoptosis or reduced rate of cell division and cyst maturation. Please clarify.
2 Is 18 C really a suboptimal temperature for oogenesis? While females raised at 18 C do lay fewer eggs per unit time early in their lives, the females are likely to retain higher levels of fertility for a longer period.

Reviewer 2

Advance summary and potential significance to field

Gandara and Drummond-Barbosa studied the effect of cold and warm temperatures on the fate of female germline and follicle cells in adult Drosophila. 25°C was chosen as the reference temperature because it is generally considered the ideal temperature for Drosophila melanogaster. The lower temperature was 18°C, a temperature that is still within the physiological range and at which fly stocks are typically kept for long periods. The high temperature of 29°C is the maximum temperature at which flies can be kept without becoming sterile. This careful analysis now describes the effect of suboptimal temperatures on female fertility and fecundity. Suboptimal temperatures reduced the rate of egg production in both cases. At low temperatures, the follicle (egg chamber) growth rate is reduced, but germline stem cells appear to be more stable, germline cysts survive better, and oocyte quality remains high for longer periods. It appears that the reproductive system ages more slowly at 18°C. At the higher temperature, early cysts die more frequently vitellogenic follicles degenerate more often, and oocyte quality drops remarkably.

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Comments for the author

The interpretation of the results is that cold temperature produces better oocyte and egg quality. This is true but the reason might be more trivial than what is mostly suggested in this manuscript. Since chemical reactions and biochemical reactions in the physiological range proceed more slowly at cold temperatures (Van 't Hoff equation), it seems that the germline and cap cells simply age more slowly, and everything takes a little (2x) longer. Most of the results obtained at low temperature can be explained by this mechanism suggesting that the effect occurs directly because of the reduced temperature and would not be imposed by a control mechanism as suggested. This more trivial alternative interpretation of the effect on fertility and fecundity, on the loss of different cells, and on the prolonged S phase would need to be ruled out. In the present manuscript, this explanation is mentioned in one sentence in the discussion (l. 402-4) and no evidence against this explanation is provided.
For the high-temperature experiments, it is important to know how effectively the 29°C temperature was controlled. The Methods section indicates that temperature and humidity were monitored daily (l. 487-8). The results of this monitoring should be included in the manuscript because the flies cannot tolerate a slightly higher temperature for very long. The same is true for humidity control because it affects the consistency of the food and thus the availability of the food.
The first section of the results suggests that during the second 5 days at 29°C (d5-d10), the high temperature has already caused too much damage to the flies as returning them to 25oC no longer restores normal egg production. This suggests that true temperature control can only be studied before this period.
However, oogenesis takes several days, so it is likely that the effect on oviposition reported in Fig. 1 reflects the increase in apoptotic germline cysts that is already observed during the first 5 days (Fig. 4).
The value of this part of the work could be improved by clearly distinguishing between the effect of elevated temperature on normal physiology (temperature control) and the effect caused by non-physiological elevated temperature (thermal damage). However, I am not sure that this is possible.
Figure 6 shows the dying vitellogenic follicles and the statistical analysis on them. In this figure, there seem to be many more dying follicles at 29°C already after 5 days. However, the text states that there is no significant difference for the survival of vitellogenic follicles at 5 and 10 days (without showing this analysis).
Thus, this statement seems inconsistent.
The effect of elevated temperature on egg quality was studied by keeping adult flies at different temperatures but allowing their eggs to develop afterward at 25°C. In this case, differences in the aging of flies kept at different temperatures were not taken into account for the interpretation of the results. Nevertheless, the effect of 29°C is considerably higher than the difference in aging. Additional contributing factors, such as male sterility and reduced egg quality, were demonstrated.
Line 304: The conclusion that these processes are male-independent does not make sense.
The authors also addressed the question of whether the temperature sensor TrpA1 (and Gr28b) might be involved in the ovarian response to warm temperature. Their results indicate a redundant function of the sensors in the protection of vitellogenic follicles during oogenesis. However, there is no evidence of the pathway through which the sensors mediate such an activity. It could be modifying physiology or behavior (e.g., by cooling the fly or directing it to a wetter, cooler location). Surprisingly, however, they also found that TrpA1(1) homozygous females had markedly improved oocyte quality compared to controls. The authors do not resolve this apparent contradiction with the effect on vitellogenic follicles.

Minor points:
Fig 1B: does 1/2A mean 1 ,2A (1 and/or 2A)?
Fig 5: Does the ß-Gal marker contain an NLS? Can it move between cyst cells?
The last sentence of the results concludes that TrpA1 mediates the effects of warm temperature on oocyte quality. This is confusing. It would be clearer to say that it mediates the negative effect of heat (as stated in the discussion at the end of p13 and beginning of p17).

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Reviewer 3

Advance summary and potential significance to field

The manuscript entitled 'Warm and cold temperatures induce distinct germline stem cell lineage responses during Drosophila oogenesis' by Gandara and Drummond-Barbosa, addresses the importance of temperature on reproduction in Drosophila melanogaster. Because of the current climate crisis, major concerns have been raised about the impacts of temperature on the reproduction of cold-blooded animals, such as insects. The manuscript reports the effects of chronic exposure of adult females to cold and warm temperatures on ovarian follicle formation and development.

The authors first show that females kept in either cold (18°C) or warm (29°C) temperature laid fewer eggs than females raised at 25°C. They established that exposure to low or high temperature differentlially affects egg production. Cold temperature improves GSC maintenance and oocyte quality, and slows down follicle growth, partly due to the extension of the S phase during cell cycle. In contrast, exposure to high temperatures causes an increase in the death of 8-cell germline cysts and of vitellogenic follicles, which to a certain extent explains the reduction of fertility of these females. Oocyte quality and male fertility are also impaired when females or males are raised at 29°C. Of note, the authors also tested the role of food consumption and male factors and found that they are mostly not responsible for the different phenotypes observed during oogenesis in females chronically exposed to cold or warm temperatures. Finally, the authors show that oocyte quality is likely to be protected at high temperature by the activity of the warm temperature receptor Trp A1.

Comments for the author

The manuscript is well-written and all conclusions are supported by the data. As the authors checked the importance of the few external factors that could have been at play to explain the reduction in egg production (food consumption, male fertility, male factors…), this manuscript clearly establishes the importance of temperature on oogenesis. This allows the authors to state that chronic exposure to cold or to warmth leads to different phenotypes and that warm temperatures are more deleterious for oogenesis than cold.
Overall, this manuscript is of broad interest, especially as the need for data about insect reproduction is becoming more and more important. The only concerns are that the work is fairly descriptive, but this is an editorial, not a scientific, matter and I found the title inappropriate.

First revision

Author response to reviewers' comments

REVIEWER 1

Reviewer 1 recognized that ***"this work is important in light of a worldwide increase in temperatures due to global warming."***

He/She, however, identified several significant issues, addressed below.

Point 1: ***"The authors conclude that raising females at 29°C results in the death of vitellogenic follicles and lowers oocyte quality while raising males at 29°C impairs male fertility (Figure 7). However, it is well-established in the literature that high temperatures decrease mating success in Drosophila.***
The authors do not adequately address this confounding factor. Hatch rates and death of vitellogenic chambers are both impacted by mating and fertilization. Observing the number of stage 14 oocytes is not an adequate substitute for directly examining laid eggs, for either the presence of sperm or an attempt at early embryogenesis. Therefore, the rigor of the manuscript would be improved if the authors determined what

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percentage of eggs were fertilized when males and females are raised at various temperatures. Subsequently, the authors should determine what component of the decrease in oocyte quality (as determined by hatch rates) or death of vitellogenic chambers is due to decreased mating."

We respectfully note that, based on our careful literature research, the reported effects of temperature (in the range of our experiments) are inconsistent owing to very variable experimental designs (i.e. how temperature exposure is done and how mating success is measured). We have included a brief summary of this literature in the revised manuscript (text lines 287-298). Also, we have performed additional experiments using males that produce GFP-labeled sperm (and examining the presence of green sperm in *y w* female spermathecae) that show that the low hatching rates at 29°C are not caused by lack of transfer of sperm to females (Fig. 8C,D and text lines 335-343; 513-515; 592-600). In addition, we measured death of vitellogenic follicles in virgin females and showed that the increased in vitellogenic degeneration is male-independent (Fig. 8G and text lines 347- 348). These new data add to the body of evidence in the original manuscript showing that mating is not significantly affected by temperature:

- Ovulation is impacted by mating; the fact that there are no significant issues with ovulation at 29°C indicate that mating is occurring. (Note: the number of stage 14 oocytes was used as a measure of ovulation, which in flies occurs before fertilization.)
- The effect of temperature on early germline cyst death and follicle growth was present in virgin or mated females (in agreement with our new data for vitellogenic degeneration), indicating that those effects are male-independent (and therefore, mating-independent).

Point 2: ***"The authors conclude that the temperature receptor TrpA1 is partially required for the decrease in oocyte quality observed at higher temperatures. Specifically, they show that TrpA1 partially rescues the oocyte quality defects observed at higher temperatures. Unfortunately, the authors examined a single null allele of TrpA1. To make this conclusion, they need to rescue this phenotype, with a transgenic rescue construct or duplication, and/or generate a second allele of TrpA1 that has the same phenotype. Similarly, the double mutant analysis of TrpA1 with Grb28b, needs to be performed with additional alleles of TrpA1 and Grb28b or the synergistic phenotype needs to be rescued with a transgenic rescue construct or duplication."***

We thank the reviewer for suggesting that we perform a rescue experiment to verify the phenotype of the null *TrpA1* mutation on oocyte quality. We conducted the rescue experiment and found that a previously published genomic rescue construct (which we have also backcrossed into the same *y w* background) does not revert the effect of the TrpA1 mutation (in fact, it makes it stronger). (Perhaps the effect is due to remaining background differences.) Therefore, we have changed our conclusion to indicate that canonical warm temperature receptors do not play a major role in the effects of warm temperature during oogenesis (Fig. S5F and text lines 352-353, 381-383, and 385-387) and deleted the corresponding part of the Discussion.

The effect on vitellogenic stages is very variable and has unclear biological significance (and we had not included it in our final model figure). Although at this point it is not a priority for our lab to invest time and effort in following up on these findings, the reviewer's comments are well taken. In response to these comments, we made a special effort in this revised manuscript to explicitly emphasize the unclear biological significance of the vitellogenic follicle findings, considerably weaken our conclusion, and remove mention of this result in the Discussion (text lines 375-377).

Point 3 (minor): ***"Page 7 figure 4. It is not clear if the authors are concluding females raised at 18 degrees have increased number of 16 cell cysts relative to wild type due to decreased apoptosis or reduced rate of cell division and cyst maturation. Please clarify."***

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We have rephrased our sentence to make it extra clear (text lines 186-189) that the decrease in apoptosis leads to increased number of 16-cell cysts.

Point 4 (minor): ***"18°C really a suboptimal temperature for oogenesis? While females raised at 18°C do lay fewer eggs per unit time early in their lives, the females are likely to retain higher levels of fertility for a longer period."***

We understand the reviewer's comment; however, we chose the word "suboptimal" for simplicity of communication given that 18°C and 29°C are not the optimal temperature for high levels of egg production in the short term, and 25°C has been traditionally considered the optimal temperature for raising *Drosophila melanogaster* in the lab. Although this is a difficult question to address, one could argue that fast reproduction of flies in nature might be advantageous (as opposed to prolonged), considering the existence of predators and other "unnatural" causes of death in the wild.

REVIEWER 2

Reviewer 2 recognized that our analysis was careful, but also had several comments that are addressed below.

Point 1: ***"The interpretation of the results is that cold temperature produces better oocyte and egg quality. This is true, but the reason might be more trivial than what is mostly suggested in this manuscript. Since chemical reactions and biochemical reactions in the physiological range proceed more slowly at cold temperatures (Van 't Hoff equation), it seems that the germline and cap cells simply age more slowly, and everything takes a little (2x) longer. Most of the results obtained at low temperature can be explained by this mechanism, suggesting that the effect occurs directly because of the reduced temperature and would not be imposed by a control mechanism as suggested. This more trivial alternative interpretation of the effect on fertility and fecundity, on the loss of different cells, and on the prolonged S phase would need to be ruled out. In the present manuscript, this explanation is mentioned in one sentence in the discussion (l. 402-4) and no evidence against this explanation is provided."***

We agree with the reviewer that it is formally possible that the interpretation of the cold temperature results could be of a thermodynamic nature [although this is a highly debated topic when it comes to reactions occurring in intact living organisms where many additional factors are at play (see Schulte, 2014 and Glazier, 2015 references in revised manuscript)] and/or due to a lower rate of aging. Regardless, more specific regulation might also be occurring (as is the case for diet, where simple nutrient limitation to every cell might have been similarly thought at face value as "the" reason why the entire organism responds to changes in diet). In any case, we think the biology of how temperature affects the ovary is interesting in and of itself regardless of the specific mechanisms, and, as usual, we are not attached to any particular model.
Nevertheless, we make it more explicit in the manuscript that effects of cold temperature could be due to changes in thermodynamics and/or slower organismal aging (text lines 112; 155-156; 165-166; 253-254).

Point 2: ***"For the high-temperature experiments, it is important to know how effectively the 29°C temperature was controlled. The Methods section indicates that temperature and humidity were monitored daily (l. 487-8). The results of this monitoring should be included in the manuscript because the flies cannot tolerate a slightly higher temperature for very long. The same is true for humidity control because it affects the consistency of the food and thus the availability of the food."***

We have now included this information more explicitly in the methods and in the supplement (Fig. S1A,B; text lines 524-526).
Point 3: ***"The first section of the results suggests that during the second 5 days at 29°C (d5-d10), the high temperature has already caused too much damage to the flies as returning them to 25°C no longer restores normal egg production. This suggests that true temperature control can only be studied before this period. However, oogenesis takes***

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several days, so it is likely that the effect on oviposition reported in Fig. 1 reflects the increase in apoptotic germline cysts that is already observed during the first 5 days (Fig. 4).

"The value of this part of the work could be improved by clearly distinguishing between the effect of elevated temperature on normal physiology (temperature control) and the effect caused by non- physiological elevated temperature (thermal damage). However, I am not sure that this is possible."

We agree with the reviewer's point, and this is the reason why we refer to most of what we observe as effect of temperature (instead of temperature control/regulation), and have now revised the title, short title, and text (text lines 120-121; 140; 349-350; 364-367; 430; 991) to be extra cautious and not mislead the readers (e.g. with the word "response") – which is never our intention. Figuring out what changes reflect actual regulatory steps, quality control mechanisms, or molecular/cellular damage will take multiple separate studies in the future.

Point 4: ***"Figure 6 shows the dying vitellogenic follicles and the statistical analysis on them. In this figure, there seem to be many more dying follicles at 29°C already after 5 days. However, the text states that there is no significant difference for the survival of vitellogenic follicles at 5 and 10 days (without showing this analysis). Thus, this statement seems inconsistent."***

We are confused by the reviewer's comment. We showed all of the data in figure 6, we described the statistical analysis, and we indicated the statistically significant differences in the graph, along with the *P* value. There is a non-statistically significant trend at 5 and 10 days, but it becomes a much larger and statistically significant difference only at 15 and 20 days. Nevertheless, we now mention this trend at days 5 and 10 in the legend of Fig. 6 (text lines 1102-1103).

Point 5: ***"The effect of elevated temperature on egg quality was studied by keeping adult flies at different temperatures but allowing their eggs to develop afterward at 25°C. In this case, differences in the aging of flies kept at different temperatures were not taken into account for the interpretation of the results. Nevertheless, the effect of 29°C is considerably higher than the difference in aging. Additional contributing factors, such as male sterility and reduced egg quality, were demonstrated."***

We appreciate the reviewer's comment, and we also point out that differences in aging rates at different temperatures could potentially be part of the mechanisms underlying differences in oogenesis, egg production, and oocyte quality at different temperatures. Biology is complex, and multiple mechanisms (so-called trivial or non-trivial) can be operating simultaneously.

Point 6: ***"Line 304: The conclusion that these processes are male-independent does not make sense."***

Please see response to Point 1 of Reviewer 1 above. We have also further clarified this conclusion in the text (text lines 321-350).

Point 7: ***"The authors also addressed the question of whether the temperature sensor TrpA1 (and Gr28b) might be involved in the ovarian response to warm temperature. Their results indicate a redundant function of the sensors in the protection of vitellogenic follicles during oogenesis. However, there is no evidence of the pathway through which the sensors mediate such an activity. It could be modifying physiology or behavior (e.g., by cooling the fly or directing it to a wetter, cooler location). Surprisingly, however, they also found that TrpA1(1) homozygous females had markedly improved oocyte quality compared to controls. The authors do not resolve this apparent contradiction with the effect on vitellogenic follicles."***

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Please see response to Point 2 of Reviewer 1 above. Regardless, please note that different steps of oogenesis are often regulated very differently by physiological factors. (For example, increased insulin signaling stimulates many stages in oogenesis, but reduced insulin/Akt signaling is required for proper metabolic maturation of the final oocyte; reviewed in Drummond-Barbosa, 2019, reference cited in the manuscript).

Point 7 (minor): ***"Fig 1B: does 1/2A mean 1, 2A (1 and/or 2A)?"***

In Figures 4 and 8, 1/2A means "late Region 1 and/or 2A". We now clarify that in the legend for Figure 4 (text line 1056).

Point 8 (minor): ***"Does the ß-Gal marker contain an NLS? Can it move between cyst cells?"***

Yes, the ß-Gal marker contains an NLS. It is possible that it moves between cyst cells; however, if it does, this is not 100% effective, as we can see partially labeled germline cysts in our analysis (e.g. see Fig. 5B).
Regardless, our analysis combines both fully and partially labeled germline cysts, and any potential transport between cells within a cyst has no effect on the results.

Point 9 (minor): ***"The last sentence of the results concludes that TrpA1 mediates the effects of warm temperature on oocyte quality. This is confusing. It would be clearer to say that it mediates the negative effect of heat (as stated in the discussion at the end of p13 and beginning of p17)."***

Please see response to Reviewer 1's Point 2 above.

REVIEWER 3

Reviewer 3 states: ***"The manuscript is well-written and all conclusions are supported by the data. As the authors checked the importance of the few external factors that could have been at play to explain the reduction in egg production (food consumption, male fertility, male factors…), this manuscript clearly establishes the importance of temperature on oogenesis. This allows the authors to state that chronic exposure to cold or to warmth leads to different phenotypes and that warm temperatures are more deleterious for oogenesis than cold.***

"Overall, this manuscript is of broad interest, especially as the need for data about insect reproduction is becoming more and more important."

We appreciate the reviewer's positive comments and the recognition that our data support our conclusions. We strive for rigor in our studies: we consistently aim for large sample sizes, quantification of all observations, careful statistical analysis, and do our best to avoid any overstatement of what our data show and to carefully word our conclusions.

He/She also express the following concerns: ***"The only concerns are that the work is fairly descriptive, but this is an editorial, not a scientific, matter and I found the title inappropriate."***

We agree that the work is descriptive, although this is a new and thorough characterization of how temperature affects the *Drosophila* ovary, which is an important foundation for future mechanistic studies by my lab and others interested in this question. Although descriptive work is often undervalued in science nowadays, any biological process needs to be carefully described before mechanistic studies are done, and high-quality descriptions are very time-consuming and rare.

In retrospect, we now realize that the word "responses" in the title could inadvertently convey the idea of highly regulated processes, when the reality is that we do not know what range of mechanisms might be mediating the effects of temperature on the ovary (potentially a combination of thermodynamic effects, changes in aging rates, stress responses, and/or

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other types of regulatory mechanisms). Therefore, we have now changed the title to “Warm and cold temperatures have distinct germline stem cell lineage effects during *Drosophila* oogenesis.”

Second decision letter

MS ID#: DEVELOP/2021/200149

MS TITLE: Warm and cold temperatures have distinct germline stem cell lineage effects during Drosophila oogenesis

AUTHORS: Ana Caroline P Gandara and Daniela Drummond-Barbosa
ARTICLE TYPE: Research Article

I am happy to tell you that your manuscript has been accepted for publication in Development, pending our standard ethics checks.

Reviewer 1

Advance summary and potential significance to field

This manuscript by Gandara and Drummond-Barbosa examines how raising females and males at sub optimally high (29 C) and low (18) temperatures impacts oocyte growth, development, and quality. While this work is important and well done it is primarily descriptive.

Comments for the author

For the most part the authors have done an excellent job addressing my comments.
I believe this manuscript lays the foundation for future work on the identification of the pathways that control the response to temperature during oogenesis. I am excited to see what follows. I have little doubt that this manuscript will be highly cited. However, the work is primarily descriptive which is unusual for a Development manuscript. This is an editorial decision.

Reviewer 2

Advance summary and potential significance to field

Gandara and Drummond-Barbosa studied the effect of cold and warm temperatures on the fate of female germline and follicle cells in adult Drosophila. 25oC was chosen as the reference temperature because it is generally considered the ideal temperature for Drosophila melanogaster. The lower temperature was 18oC, a temperature that is still within the physiological range and at which fly stocks are typically kept for long periods. The high temperature of 29oC is the maximum temperature at which flies can be kept without becoming sterile. This careful analysis now describes the effect of suboptimal temperatures on female fertility and fecundity. Suboptimal temperatures reduced the rate of egg production in both cases. At low temperatures, the egg chamber growth rate is reduced, but germline stem cells appear to be more stable germline cysts survive better, and oocyte quality remains high for longer periods. At the higher temperature early cysts die more frequently, vitellogenic follicles degenerate more often, and oocyte quality drops remarkably. The authors also show that diet, male factors, and canonic temperature sensors do not play a major role in this response.

Comments for the author

No further revisions are required.

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Reviewer 3

Advance summary and potential significance to field

The manuscript entitled ‘Warm and cold temperatures induce distinct germline stem cell lineage responses during Drosophila oogenesis’ by Gandara and Drummond-Barbosa, addresses the importance of temperature on reproduction in Drosophila melanogaster. Because of the current climate crisis, major concerns have been raised about the impacts of temperature on the reproduction of cold-blooded animals, such as insects. The manuscript reports the effects of chronic exposure of adult females to cold and warm temperatures on ovarian follicle formation and development.

Comments for the author

I am fully satisfied by the answers provided by the authors to all the comments from the reviewers. I support publication of this work.

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