Centriole and Golgi microtubule nucleation are dispensable for the migration of human neutrophil-like cells

Lucas Klemm, Ryan Denu, Laurel Hind, Briana Rocha-Gregg, Mark Burkard, and Anna Huttenlocher

Corresponding author(s): Anna Huttenlocher, University of Wisconsin

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(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)

RE: Manuscript #E21-02-0060
TITLE: Centriole and Golgi microtubule nucleation are dispensable for the migration of human neutrophil-like cells

Dear Anna,

Your manuscript, entitled "Centriole and Golgi microtubule nucleation are dispensable for the migration of human neutrophil-like cells" has been seen by two referees whose verbatim comments are enclosed. As you will see, both referees find the study of significant interest in principle, and both recommended for publication in MBOC, with suitable revisions. Both referees asked for quantification of many of the results and better evidence to support some of the conclusions. We look forward to receiving your revised manuscript and a letter indicating your response to each of the referees' comments in the near future.

Sincerely,

Denise Montell
Monitoring Editor
Molecular Biology of the Cell

Dear Dr. Huttenlocher,

The review of your manuscript, referenced above, is now complete. The Monitoring Editor has decided that your manuscript is not acceptable for publication at this time, but may be deemed acceptable after specific revisions are made, as described in the Monitoring Editor's decision letter above and the reviewer comments below.

A reminder: Please do not contact the Monitoring Editor directly regarding your manuscript. If you have any questions regarding the review process or the decision, please contact the MBoC Editorial Office (mboc@ascb.org).

When submitting your revision include a rebuttal letter that details, point-by-point, how the Monitoring Editor's and reviewers' comments have been addressed. (The file type for this letter must be "rebuttal letter"; do not include your response to the Monitoring Editor and reviewers in a "cover letter.") Please bear in mind that your rebuttal letter will be published with your paper if it is accepted, unless you haveopted out of publishing the review history.

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In preparing your revised manuscript, please follow the instruction in the Information for Authors (www.molbiolcell.org/info-for-authors). In particular, to prepare for the possible acceptance of your revised manuscript, submit final, publication-quality figures with your revision as described.

To submit the rebuttal letter, revised manuscript, and figures, use this link: Link Not Available

Please contact us with any questions at mboc@ascb.org.

Thank you for submitting your manuscript to Molecular Biology of the Cell. We look forward to receiving your revised paper.

Sincerely,

Eric Baker
Journal Production Manager
MBoC Editorial Office
mbc@ascb.org

Reviewer #1 (Remarks to the Author):

In this manuscript, the authors explored the role of the MTOC in neutrophil motility. The authors specifically focused on determining the role of centrioles as the dominant and Golgi as the alternative MTOC in regulating the directional motility of neutrophil-like differentiated PLB-985 cells. Using a pharmacological inhibitor for centrosome depletion and CRISPR/Cas9 technique to knockout centriolar assembly protein (SAS6), the authors found that centrioles are not essential for microtubule organization and neutrophil motility, instead, elimination of centrioles promoted greater speed of PLB-985 cells migrating towards fMLF. By knocking out GM130, the authors further showed that the inhibition of Golgi-mediated microtubule nucleation is also dispensable for directional motility.
This is an interesting study that brings forth important findings. However, the following comments should be considered to make the study more comprehensive and insightful.
Major comments:
1. It is very difficult to assess the directionality of migration in Movies S1, S3, and S4. Which cells in the movies were tracked? The tracks should be shown on the movies and more information should be given about the geometry of the chemotactic chamber. It appears that the cells are migrating directionally only in the bottom narrow channel.
2. To compare the behavior of cells under the different conditions, the directionality of chemotaxing cells should be quantified for all of the track plots as chemotactic index. Why do the centrinone-treated cells have fewer tracks than the control cells in Fig 1D? Are there less cells moving directionally? The blebbistatin-treated cells appear to have better directional migration than the control cells (Fig 2E), although here again there appears to be less tracks. Quantification should clarify this.
3. The distance travelled in the centrinone-treated cells appears greater than control cells in the undergarose assay (Fig 1G). Here again, the migration speed and chemotaxis index should be quantified.
4. The IF images in Figure 3B, 4E, and 5D show an increase in microtubule content with the depletion of centrosomes and/or Golgi-specific MTOC function. This should be quantified. Similarly, the treated cells appear much larger. The surface area and uropod length should be quantified.
5. The changes in MT network may underlie the improved speed of centrosome-less cells. This should be tested using microtubule disrupting drug like nocodazole or colchicine.
6. Phase contrast images should be added to figure 3B, 4E, and 5D to clearly show the cell periphery and front-back.
7. In Fig. 5B, it is not clear that the IF signal for centrin is specific. The nucleus size also appears less lobulated in the SAS6 knockouts.
8. Does centrosome manipulation alter cell adhesion in PLB-985 cells as observed in mesenchymal cells?
9. Whether GM130 knockout disrupts AKAP450 localization in Golgi of PLB-985 should be validated. The presence of intact centrosomes in the knockouts should also be confirmed.
Minor comments:
1. The authors incorrectly use the term rose plots to describe the track plots.
2. The track plots should have defined axes.
3. Please review figure legends and provide number of repeats and number of cells analyzed for all data presented.
4. It is very difficult to see the DAPI signal in the "merge with DAPI" images in Fig. 4E and 5D.
5. The GM130 data should be moved to the end of the ms.

Reviewer #2 (Remarks to the Author):

In their manuscript titled "Centriole and Golgi microtubule nucleation are dispensable for the migration of human neutrophil-like cells", Klemm and colleagues describe an analysis of the effect of depeletion of microtubule organizing centers on the directed cell migration of neutrophil-like cells. Surprisingly, they find that cell speed is increased and directionality is unaffected. The work represents new findings advancing our understanding of the role of microtubules and microtubule organization in neutrophil chemotaxis. While the conclusion about increased speed is well supported, some of the smaller conclusions need further clarification or support.

A weakness of this study is that the authors did not fully disrupt MTOC formation. The cells always seemed to maintain some type of MTOC close to the center of the cell. However, they identified a clear and interesting phenotype for centrosome depletion, and they confirmed it through both chemical and genetic approaches.

My detailed comments include:
1.) The measurements of directed cell migration (Figures 1D,1F,2E,3D,4F) should be quantified. While the aligned cell track plots give a qualitative answer that directionality is similar, quantification is necessary to come to a clear conclusion. Since cell speed is affected, a purely direction-based metric such as the angle of cell movement relative to the gradient would be the most informative.

2.) The conclusion that the effect on cell speed is not due to cell size or polyploidy is not sufficiently supported. The authors addressed this with an elegant experiment using blebbistatin as an alternate way to interfere with cell division. However, the blebbistatin treatment also appears to increase speed (Figure 2D) to a similar extent as caused by Centrinone. While the authors did not find statistical significance for the effect of blebbistatin on cell speed, the effect is nonetheless apparent in their data, and the lack of statistical significance does not mean the effect is not real (just that it has not been conclusively

demonstrated). The authors should increase their statistical replicates to determine whether blebbistatin treatment recapitulates the effect on cell speed caused by Centrinone.

3.) Previous studies in neutrophil-like cells have focused on the connection between microtubules and migration, with a major conclusion being that microtubules limit RhoA signaling by sequestering the GEF GEF-H1. This study is an interesting complement to previous studies by focusing on the role of MTOCs and microtubule organization rather than mass. However, it would still be interesting to know if the effects observed in this study are working through this same pathway. Does MTOC depletion affect the mass of polymerized microtubules, and does its affect on migration speed work through Rho family GTPase signaling? Answering these questions is not necessary to verify the claims made in the manuscript, but it would help connect the study to previous work in the field.

Smaller points:
1.) In line 179, the authors say that cells "showed a polarized network". It is clear from context that this is referring to the microtubule network, but it would be better to state this explicitly.

2.) In line 206, the authors say "the loss of both centrosomes and Golgi MTOCs did not impair directed migration". However, it is not clear that the authors really removed Golgi MTOCs. It might be better to say GM130-dependent MTOCs or something similar. The images in Figure 4C appear to show Golgi-localized or at least Golgi-adjacent MTOCs in the GM130 KO cell line, perhaps through an alternate pathway?

Dear Editor

We thank the reviewers for their comments on our manuscript. Below we provide a point-by-point response to review. We think that the revisions have significantly improved the manuscript.

Reviewer 1

Thank you for your enthusiasm and comments about our manuscript.

In this manuscript, the authors explored the role of the MTOC in neutrophil motility. The authors specifically focused on determining the role of centrioles as the dominant and Golgi as the alternative MTOC in regulating the directional motility of neutrophil-like differentiated PLB-985 cells. Using a pharmacological inhibitor for centrosome depletion and CRISPR/Cas9 technique to knockout centriolar assembly protein (SAS6), the authors found that centrioles are not essential for microtubule organization and neutrophil motility, instead, elimination of centrioles promoted greater speed of PLB-985 cells migrating towards fMLF. By knocking out GM130, the authors further showed that the inhibition of Golgi-mediated microtubule nucleation is also dispensable for directional motility.

This is an interesting study that brings forth important findings. However, the following comments should be considered to make the study more comprehensive and insightful.

Major comments:
1. It is very difficult to assess the directionality of migration in Movies S1, S3, and S4. Which cells in the movies were tracked? The tracks should be shown on the movies and more information should be given about the geometry of the chemotactic chamber. It appears that the cells are migrating directionally only in the bottom narrow channel.

The geometry of the device is previously published and described in (Yamahashi *et al., Biomed Microdevices*. 2015 Oct;17(5):100). All cells within the field of view were tracked and a threshold was applied (see methods for specifics) to remove dead/immobile cells. This is clarified in the methods section.

2. To compare the behavior of cells under the different conditions, the directionality of chemotaxing cells should be quantified for all of the track plots as chemotactic index. Why do the centrinone-treated cells have fewer tracks than the control cells in Fig 1D? Are there less cells moving directionally? The blebbistatin-treated cells appear to have better directional migration than the control cells (Fig 2E), although here again there appears to be less tracks. Quantification should clarify this.

Chemotactic index analysis was performed on the tracked cells. Please see the updated figures, figure legends, and main text for data and interpretation. We found that chemotactic migration was also increased with centriole depletion.

3. The distance travelled in the centrinone-treated cells appears greater than control cells in the underagarose assay (Fig 1G). Here again, the migration speed and chemotaxis index should be quantified.

The underagarose data was removed from the manuscript.

4. The IF images in Figure 3B, 4E, and 5D show an increase in microtubule content with the depletion of centrosomes and/or Golgi-specific MTOC function. This should be quantified. Similarly, the treated cells appear much larger. The surface area and uropod length should be quantified.

We agree with the reviewer that further quantification could be beneficial. We experimented with different quantification methods and due to the differences in cell shape and density those analyses were not feasible in our model because of the compact morphology of control neutrophils. To address this question further, we added new data showing that microtubules are necessary for the phenotype (revised figure 3C).

5. The changes in MT network may underlie the improved speed of centrosome-less cells. This should be tested using microtubule disrupting drug like nocodazole or colchicine.

We performed microtubule disruption experiments with nocodazole and found that the effects were microtubule dependent (revised figure 3C).

6. Phase contrast images should be added to figure 3B, 4E, and 5D to clearly show the cell periphery and front-back.

Phase contrast images were not acquired with these data and we hope it is ok to include the images as presented.

7. In Fig. 5B, it is not clear that the IF signal for centrin is specific. The nucleus size also appears less lobulated in the SAS6 knockouts.

The centrin staining is difficult in neutrophil-like cells with this antibody, but we had reproducible results. In general, the nuclei of PLB-985 cells are not very lobular. Any change in lobularity is likely related to the apparent increased nuclear size.

8. Does centrosome manipulation alter cell adhesion in PLB-985 cells as observed in mesenchymal cells?

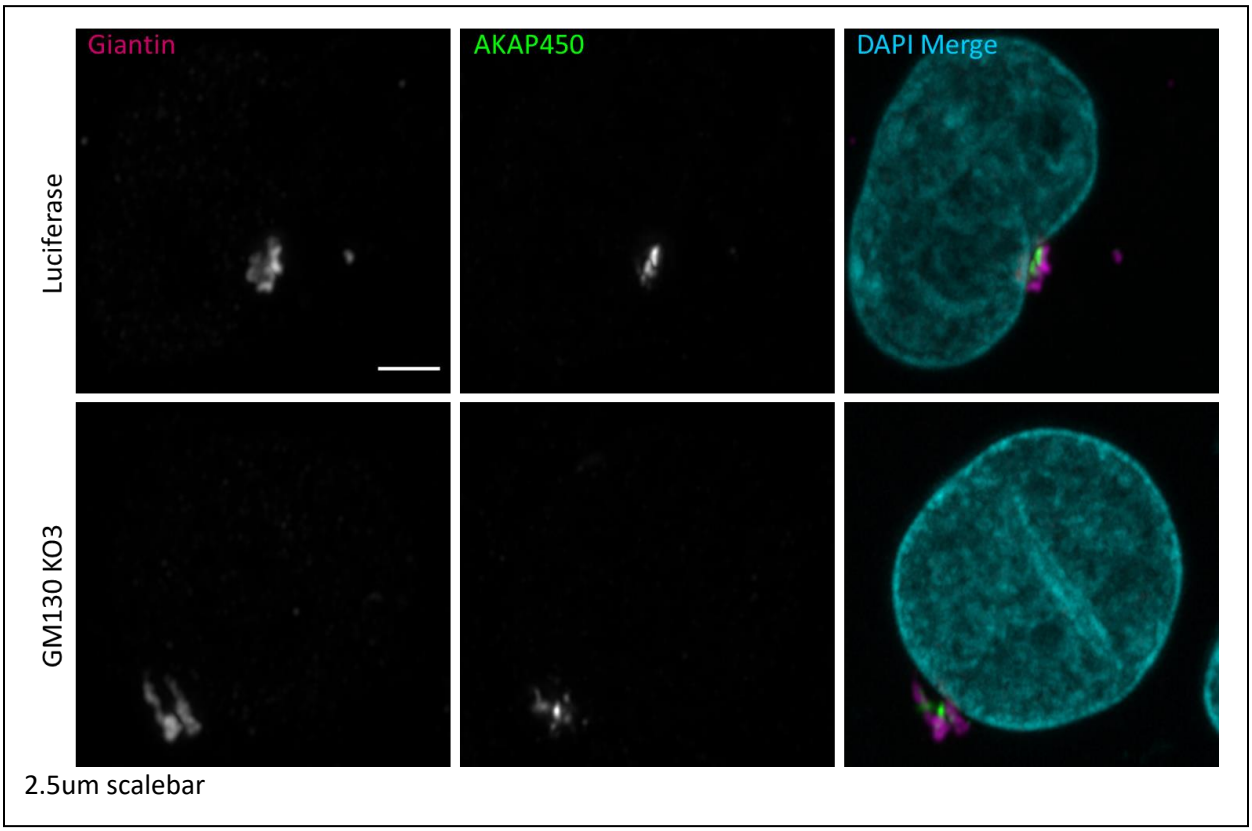
It would be interesting to see whether centrosome manipulation alters the adhesive capability of neutrophil-like cells. However, we think this is beyond the scope of the current paper. Additionally, neutrophil migration in a 3D

environment can be largely adhesion-independent, so this would not add significantly to the paper.

9. Whether GM130 knockout disrupts AKAP450 localization in Golgi of PLB-985 should be validated. The presence of intact centrosomes in the knockouts should also be confirmed.

We performed immunofluorescence for AKAP450 together with giantin. Please see representative images below of the GM130 deficient cell lines versus luciferase control. In contrast to what we expected, it appears that AKAP450 signal is still largely intact in an area near the Golgi. This suggests that GM130 may be dispensable for AKAP450 localization in neutrophil-like cells and either an alternative mechanism retains AKAP450. We discuss this issue in the text in terms of the lack of specificity of AKAP450 staining.

The centrosome is located near the Golgi and AKAP450 is known to localize there as well, so that is a possible component retaining AKAP450 proximally. More work would need to be done to determine whether GM130 is necessary for AKAP450 retention at the Golgi and all other possible MTOCs need to be disrupted simultaneously.



Minor comments:

1. The authors incorrectly use the term rose plots to describe the track plots.

The text was revised.

2. The track plots should have defined axes.

The axes of the track plots are now annotated for clarity.

3. Please review figure legends and provide number of repeats and number of cells analyzed for all data presented.

The number of repeats and cells analyzed were added to the figure legends.

4. It is very difficult to see the DAPI signal in the "merge with DAPI" images in Fig. 4E and 5D.

The DAPI channel was adjusted for better visual clarity.

5. The GM130 data should be moved to the end of the ms.

This section was moved to the end of the manuscript.

Reviewer 2,

Thank you for your enthusiasm.

In their manuscript titled "Centriole and Golgi microtubule nucleation are dispensable for the migration of human neutrophil-like cells", Klemm and colleagues describe an analysis of the effect of depletion of microtubule organizing centers on the directed cell migration of neutrophil-like cells. Surprisingly, they find that cell speed is increased and directionality is unaffected. The work represents new findings advancing our understanding of the role of microtubules and microtubule organization in neutrophil chemotaxis. While the conclusion about increased speed is well supported, some of the smaller conclusions need further clarification or support.

A weakness of this study is that the authors did not fully disrupt MTOC formation. The cells always seemed to maintain some type of MTOC close to the center of the cell. However, they identified a clear and interesting phenotype for centrosome depletion, and they confirmed it through both chemical and genetic approaches.

My detailed comments include:
1.) The measurements of directed cell migration (Figures 1D,1F,2E,3D,4F) should be quantified. While the aligned cell track plots give a qualitative answer that directionality is similar, quantification is necessary to come to a clear conclusion. Since cell speed is affected, a purely direction-based metric such as the angle of cell movement relative to the gradient would be the most informative.

We agree with the reviewer. We were not able to fully disrupt the MTOC. However, partial depletion led to increased motility suggesting that this is an inhibitory mechanism. This is an important new finding that adds to the field.

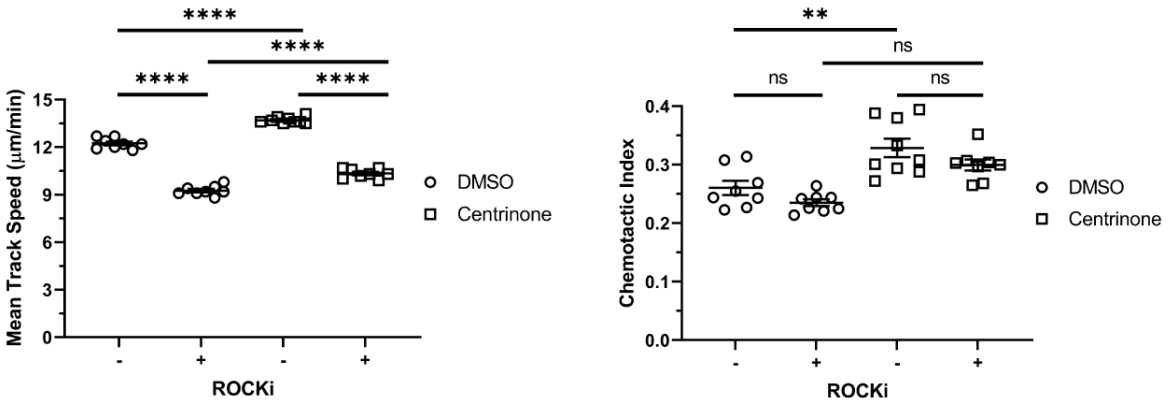
Chemotactic index analysis was performed on the tracked cells. Please see the updated figures, figure legends, and main text for data and interpretation.

2.) The conclusion that the effect on cell speed is not due to cell size or polyploidy is not sufficiently supported. The authors addressed this with an elegant experiment using blebbistatin as an alternate way to interfere with cell division. However, the blebbistatin treatment also appears to increase speed (Figure 2D) to a similar extent as caused by Centrinone. While the authors did not find statistical significance for the effect of blebbistatin on cell speed, the effect is nonetheless apparent in their data, and the lack of statistical significance does not mean the effect is not real (just that it has not been conclusively demonstrated). The authors should increase their statistical replicates to determine whether blebbistatin treatment recapitulates the effect on cell speed caused by Centrinone.

We agree with the reviewer; on re-analysis we found significant differences in migration with blebbistatin—although the effects are not as significant as what we see with centrinone or SAS6 KO. We adjusted the text to address this issue and to include these caveats.

3.) Previous studies in neutrophil-like cells have focused on the connection between microtubules and migration, with a major conclusion being that microtubules limit RhoA signaling by sequestering the GEF GEF-H1. This study is an interesting complement to previous studies by focusing on the role of MTOCs and microtubule organization rather than mass. However, it would still be interesting to know if the effects observed in this study are working through this same pathway. Does MTOC depletion affect the mass of polymerized microtubules, and does its effect on migration speed work through Rho family GTPase signaling? Answering these questions is not necessary to verify the claims made in the manuscript, but it would help connect the study to previous work in the field.

We found that the effect works through microtubules (Figure 3C). We also performed ROCK inhibition experiments using the ROCK inhibitor, Y-27632. These results do not add significantly to the manuscript (see figure below), since ROCK inhibition does not seem to affect the increased directed migration specifically.



ROCK inhibition of centrinone-treated dPLB-985 cells. Mean track speed and chemotactic index of Y-27632-treated (10 µM for 1 hour before tracking) dPLB-985 cells +/- centrinone (data displayed as mean + SEM; N=3 repeats, n=9 devices, x3,711-4,541 cells). Significance was determined by mixed-effects REML regression with a Satterthwaite degrees of freedom approximation. n.s. = not significant, **p<0.01, ****p<0.0001.

Smaller points:

1.) In line 179, the authors say that cells "showed a polarized network". It is clear from context that this is referring to the microtubule network, but it would be better to state this explicitly.

The text has been edited accordingly.

2.) In line 206, the authors say "the loss of both centrosomes and Golgi MTOCs did not impair directed migration". However, it is not clear that the authors really removed Golgi MTOCs. It might be better to say GM130-dependent MTOCs or something similar. The images in Figure 4C appear to show Golgi-localized or at least Golgi-adjacent MTOCs in the GM130 KO cell line, perhaps through an alternate pathway?

The text has been edited accordingly.

RE: Manuscript #E21-02-0060R
TITLE: "Centriole and Golgi microtubule nucleation are dispensable for the migration of human neutrophil-like cells"

Dear Anna:

Thank you for submitting your revised manuscript entitled "Centriole and Golgi microtubule nucleation are dispensable for the migration of human neutrophil-like cells." We believe your findings will be of significant interest and are interested in publishing it. Please address the few remaining reviewer suggestions. We look forward to receiving your revised manuscript and a letter indicating your response to the referee in the near future. There should be no need for further review.

Sincerely,
Denise Montell
Monitoring Editor
Molecular Biology of the Cell

Dear Dr. Huttenlocher,

The review of your manuscript, referenced above, is now complete. The Monitoring Editor has decided that your manuscript requires minor revisions before it can be published in Molecular Biology of the Cell, as described in the Monitoring Editor's decision letter above and the reviewer comments (if any) below.

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In preparing your revised manuscript, please follow the instruction in the Information for Authors (www.molbiolcell.org/info-for-authors). In particular, to prepare for the possible acceptance of your revised manuscript, submit final, publication-quality figures with your revision as described.

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Thank you for submitting your manuscript to Molecular Biology of the Cell. Please do not hesitate to contact this office if you have any questions.

Sincerely,

Eric Baker
Journal Production Manager
MBoC Editorial Office
mbc@ascb.org

Reviewer #2 (Remarks to the Author):

The authors' revised manuscript appropriately addressed all of my concerns from their initial submission. This work provides an interesting new investigation of the role of MTOCs in neutrophil migration.

I do have a few small comments for the authors in preparing their final version for publication:

1.) I would encourage the authors to consider including the AKAP450 staining data that was included in the response to reviewers as supplementary material. The AKAP450 result was surprising, and may be useful for future groups interested in the role and localization of the Golgi and MTOCs in neutrophils.

2.) I am not completely convinced by the interpretation of the Nocodazole data. Centrinone treatement increases speed, and Nocodazole treatment decreases speed. However, Centrinone treatment still appears to significantly increase cell speed in the presence of Nocodazole. This suggests that part of the mechanism may be microtubule-independent. To clarify the depedence on microtubules, the authors could compare the fold-increase in speed caused by Centrinone in the presence vs absence of Nocodazole. By eye, it looks like the increase in speed is smaller in the presence of Nocodazole, but a more direct comparison would make this more clear.

3.) In lines 186-188, the authors state that Centrinone did not affect chemotactic index in GM130 KO cells. While the difference was not statistically significant, the mean chemotactic index is increased. The authors cannot conclude that there is no effect, only that the they have not demonstrated a statistically significant effect.

Response to review

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1.) I would encourage the authors to consider including the AKAP450 staining data that was included in the response to reviewers as supplementary material. The AKAP450 result was surprising, and may be useful for future groups interested in the role and localization of the Golgi and MTOCs in neutrophils.

We have now included this data in figure S1.

2.) I am not completely convinced by the interpretation of the Nocodazole data. Centrinone treatement increases speed, and Nocodazole treatment decreases speed. However, Centrinone treatment still appears to significantly increase cell speed in the presence of Nocodazole. This suggests that part of the mechanism may be microtubule-independent. To clarify the depedence on microtubules, the authors could compare the fold-increase in speed caused by Centrinone in the presence vs absence of Nocodazole. By eye, it looks like the increase in speed is smaller in the presence of Nocodazole, but a more direct comparison would make this more clear.

We have revised the text to indicate that part of the mechanism may be microtubule independent.

3.) In lines 186-188, the authors state that Centrinone did not affect chemotactic index in GM130 KO cells. While the difference was not statistically significant, the mean chemotactic index is increased. The authors cannot conclude that there is no effect, only that the they have not demonstrated a statistically significant effect.

We have revised the text accordingly.

RE: Manuscript #E21-02-0060RR
TITLE: "Centriole and Golgi microtubule nucleation are dispensable for the migration of human neutrophil-like cells"

Dear Dr. Huttenlocher:

I am pleased to accept your manuscript for publication in Molecular Biology of the Cell.

Thank you for revising your manuscript. We are now happy to accept it for publication. Thank you for submitting this excellent work to MBoC!

Sincerely,
Denise Montell
Monitoring Editor
Molecular Biology of the Cell

Dear Dr. Huttenlocher:

Congratulations on the acceptance of your manuscript.

A PDF of your manuscript will be published on MBoC in Press, an early release version of the journal, within 10 days. The date your manuscript appears at www.molbiolcell.org/toc/mboc/0/0 is the official publication date. Your manuscript will also be scheduled for publication in the next available issue of MBoC.

Within approximately four weeks you will receive a PDF page proof of your article.

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We are pleased that you chose to publish your work in MBoC.

Sincerely,

Eric Baker
Journal Production Manager
MBoC Editorial Office
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