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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 83280

Title: Mechanism of ELL-associated factor 2 and vasohibin 1 regulating invasion, migration, and angiogenesis in colorectal cancer

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05382551
Position: Editorial Board
Academic degree: PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Spain
Author's Country/Territory: China

Manuscript submission date: 2023-01-18

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-02-25 09:31

Reviewer performed review: 2023-02-25 09:40

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The article is within the scope of the journal. It deals with an interesting topic. It is well written. The reading is fluent. Presents an experiment describing the materials, methods, results as well as a discussion. The article should be improved in several aspects: a) Extend the state of the art. b) Establish some conclusions and lines of future work. c) Improve the discussion to compare the work presented with other similar works, establishing the advances and limitations of the work presented.

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Reviewer's code: 05601558
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2023-01-18

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-03-04 05:40

Reviewer performed review: 2023-03-05 05:57

Review time: 1 Day

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This study aimed to investigate the expression of Vasohibin 1 (VASH1) in colorectal cancer (CRC) and its correlation with the expression of ELL-associated factor 2 (EAF2). The study found that EAF2 was down-regulated and VASH1 was up-regulated in advanced CRC tissue, and the expression levels of EAF2 and VASH1 were positively correlated. Furthermore, overexpression of EAF2 inhibited the activity of signal transducer and activator of transcription 3 (STAT3)/transforming growth factor beta 1 (TGF-β1) pathway by up-regulating the expression of VASH1, which inhibited cell invasion, migration, and angiogenesis in vitro. These findings suggest that EAF2 and VASH1 may serve as new diagnostic and prognostic markers for CRC, and provide a potential therapeutic target for the STAT3/TGF-β1 pathway in CRC. The study complements the understanding of the mechanism of EAF2 and VASH1 in CRC cells and provides new ideas for the development of targeted therapies for CRC. Comments: -for all Western blot figures, densitometry readings/intensity ratio of each band should be included; the whole Western blot showing all bands and molecular weight markers should be included in the Supplementary Materials; gene silencing

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experiments should use at least two gene-specific siRNAs The wound healing scratch assay is a widely used in vitro method to study cell migration and wound closure. However, there are some limitations associated with this assay, including: Variability in wound creation: The scratch wound is created manually, which can lead to variability in the size and shape of the wound. This can affect the reproducibility of the assay and the accuracy of the results. Limited control over cell behavior: The assay does not allow for precise control over cell behavior, such as directionality and migration rate. Cells may also undergo proliferation or apoptosis during the course of the assay, which can affect the interpretation of the results. Insensitivity to subtle changes: The assay may not be sensitive enough to detect subtle changes in cell migration or wound closure, particularly in cases where the cells are slow-moving or the wound is small. Lack of 3D context: The assay is performed in a 2D environment, which does not fully recapitulate the complexity of the in vivo wound healing process, where cells interact with each other and with the extracellular matrix in a 3D context. Difficulty in quantification: Quantifying wound closure can be subjective and time-consuming. There is also a risk of bias or error when manually measuring the width of the wound over time. The limitations of invasion and migration assays include the fact that they do not necessarily represent the true in vivo behavior of cells. In vitro assays cannot fully mimic the complex interactions between cells and the extracellular matrix, and the three-dimensional nature of the in vivo environment. Additionally, the results of these assays can be influenced by factors such as cell seeding density, serum concentration, and experimental conditions. Quantification of cell invasion and migration also has limitations. Manual counting of cells can be time-consuming and subjective, while automated methods may not always accurately distinguish between live and dead cells, or may be affected by artifacts such as debris or scratches. Furthermore, the choice of quantification method can depend on the specific assay being used, and different

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methods may have varying levels of sensitivity and reproducibility. Overall, the authors aimed to investigate the correlation between the expression of Vasohibin 1 (VASH1) and ELL-associated factor 2 (EAF2) in colorectal cancer (CRC) and their potential as diagnostic and prognostic markers and therapeutic targets. The study found that VASH1 was upregulated and EAF2 was downregulated in advanced CRC tissue, and their expression levels were positively correlated. The overexpression of EAF2 inhibited the activity of the STAT3/TGF-β1 pathway, which inhibited cell invasion, migration, and angiogenesis in vitro. These findings suggest that EAF2 and VASH1 may serve as new diagnostic and prognostic markers for CRC, and provide a potential therapeutic target for the STAT3/TGF-β1 pathway in CRC. The study suggests that EAF2 and VASH1 may serve as potential therapeutic targets for the STAT3/TGF-β1 pathway in CRC. It is important to note that targeting immunomicroenvironment (i.e. CTLA-4) also aim at novel approaches related to the authors findings: is a type of immunotherapy that aims to enhance the immune system's ability to fight cancer by blocking an inhibitory checkpoint. Therefore, targeting CTLA-4 may have a complementary effect on the therapeutic targets identified in the first study, as it could enhance the immune response against CRC cells and potentially increase the efficacy of therapies targeting EAF2 and VASH1. However, further research is needed to investigate the potential synergistic effects of these different therapeutic approaches in the context of CRC (please refer to PMID: 34067631 and expand accordingly).

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Reviewer's code: 05776275
Position: Peer Reviewer
Academic degree: PhD

Professional title: Research Associate

Reviewer's Country/Territory: United Kingdom

Author's Country/Territory: China

Manuscript submission date: 2023-01-18

Reviewer chosen by: Dong-Mei Wang

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Review time: 13 Days and 6 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
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Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors hypothesised the influence of TGF-β1 on VASH1. The manuscript shows the possible functional role and mechanism of VASH1-mediated TGF-β1 related pathway in CRC The study suggests that EAF2 and VASH1 may serve as new diagnostic and prognostic markers for CRC, and provides a clinical basis for exploring new biomarkers for CRC. This study complements the mechanism of EAF2 in CRC cells, enriches the role and mechanism of CRC cell-derived VASH1, and provides a new possible subtype of CRC as a therapeutic target of STAT3/TGF-β1 pathway