OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://brieflands.com/briefland/knowledgebase/category/tree.html#opr.html

International Journal of Cancer Management
Article DOI: 10.5812/ijcm.105436
Published in: International Journal of Cancer Management: 13(8); e105436

Peer Review Report for "A Doctrine of Ovarian Cancer Translational Research Needs Revisiting"

Author(s): Makhdoom Sarwar, Peter Sykes, John J Evans

Review Timeline:

Submit Date: 26 May 2020
Revised Date: 23 Jun 2020
Accepted Date: 27 Jun 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (0) 30 May 2020

Dear EIC
The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

REFEREE: EIC | **Revision** (0) 30 May 2020

Dear authors,
Please revise your manuscript according to the associate editor's comments.
Thanks

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

CORRESPONDENCE:
A doctrine of ovarian cancer translational research needs revisiting.

Makhdoom Sarwar[1], Peter Sykes[1], John J Evans[1]

[1]*Department of Obstetrics and Gynaecology, University of Otago, Christchurch, 2 Riccarton Avenue, Christchurch 8011, New Zealand;*

Corresponding author

Dr. Makhdoom Sarwar
Department of Obstetrics & Gynaecology,

University of Otago Christchurch,

Christchurch. New Zealand

Cell: +64 22 0287026
Email: mak.sarwar@otago.ac.nz
makmedicine@hotmail.com

LETTER

Ovarian cancers, often diagnosed with stage III/IV disease, recur frequently and eventually become resistant to standard chemotherapy. Despite an improvement in our understanding of ovarian cancer causes, survival rates have remained consistently low due to the lack of early symptoms. The 5-year survival rate in patients with an advanced stage (FIGO stage III and IV) is less than 30% as therapies become ineffective in treating metastatic ovarian cancer [1]. Most epithelial ovarian cancers are of high-grade serous (HGS-OV) histology. Little is known about the pathogenesis of HGS-OV cancer because of the late-stage presentation in most cases, due to its rapid dissemination. However, there is now extensive evidence that most HGS-OV cancers arise from serous tubal intraepithelial carcinoma (STIC) in the distal region (fimbria) of fallopian tube epithelium [2,3]. Other ovarian cancer subtypes are also thought to arise from non-ovarian tissue sources such as endometrioid and clear cell derived from endometriosis, whereas mucinous is often a metastasis from a gastrointestinal source [4,5]. This preliminary travel may imply that migration is a very early process in the tumourigenesis even before the onset of the primary tumour and thus indicative of adhesion mechanisms being involved in the disease in a very early stage. It is intriguing to wonder how much oncogenic potential tumour initiating cells (TICs) carry before adhering and colonising in the ovarian tissue. Thus, ovarian tissue provides a breeding ground for these incoming highly invasive tumour cells, which is indicative of ovarian tissue

being rich in resources required to hold and nurture the tumourigenic process.

Disease progression is followed by another invasion event but this time in an opposite direction, from the ovary to distant organs. Ovarian cancer typically metastasizes either directly to the adjacent organs or through the dissemination of exfoliated tumour cells into the peritoneum, in contrast to most of the other cancer types where lymph nodes are usually involved. Additionally, recurrent or late disease tumour cell clusters floating in the ascitic fluid show distinct expression of adhesion complex-related proteins and are often chemoresistant [6]. All these observations suggest that adhesion-related molecules (ARMs) may be assigned far more therapeutic importance than they currently enjoy.

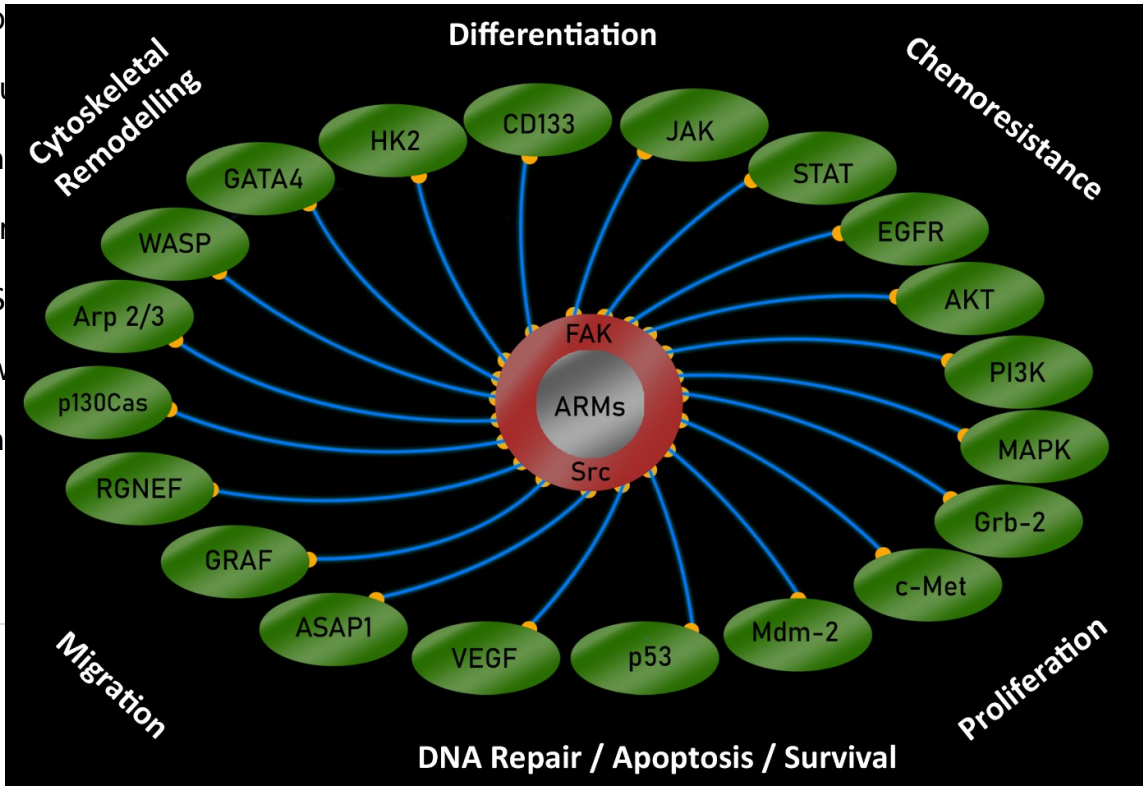
Non-receptor tyrosine kinases, such as focal adhesion kinase (FAK) and Src are the key molecules of the focal adhesion system, which is a conduit of outside-to-inside signalling. Upregulation of FAK and Src have been reported in ovarian cancer. In particular, FAK [7] and Src [8] activity are much higher in advanced disease and are associated with poor survival rates. Notably, FAK and Src mutually activate each other. This pair of tyrosine kinases regulate intracellular signalling mechanisms associated with chemoresistance in ovarian cancer such as MAPK and PI3K/AKT [9]. Ovarian cancer is a heterogeneous disease with several distinct malignant populations and often have stem cell-like cells within the tumour core or distant. A huge array of reports indicated that these immortal cancer stem cells (CSCs) are capable of self-renewal, pluripotency, and responsible for

the recurrence and the resistance to clinical interventions. Accumulating evidence suggests that FAK/Src signalling also regulates stemness via several mechanisms and the inhibition of which reduce stemness in cancer cells via interacting stem cell markers such as CD133 [10].

A phase II trial of dasatinib (Src inhibitor) as a monotherapy showed minimal therapeutic value [11]. However, Src inhibitors in combination with microtubule stabilizers or platinum-based drugs block angiogenesis, invoke caspase-9 dependent activation of the intrinsic pathway, and downregulate cell proliferation markers and therefore are likely to induce a significant increase in drug sensitivity in ovarian cancers [12]. As a single agent treatment, FAK inhibition also demonstrated a reduction in angiogenesis and increase in paclitaxel sensitivity [7]. Even though these and several other studies indicated that regulating adhesion-associated tyrosine kinases (AATKs) improve drug sensitivity in ovarian cancer, these are not yet adequately included in larger clinical trials. Bevacizumab, a non-receptor tyrosine kinase inhibitor, is approved for the treatment of epithelial ovarian cancers, and may reduce angiogenesis and tumour burden. However, it is unclear whether anti-angiogenic therapy reduces the distant metastasis due to the unorthodox dissemination of ovarian cancer. In 2019, out of $168 million of NIH funding for ovarian cancer, very little was funded towards the multi-targeting approach-based projects, and AATKs were barely seen. Worldwide, a significant number of multi-targeted studies continually explore MEK, PI3K, mTOR HER2, PARP inhibitors and some cell cycle and immune checkpoint inhibitors in various combinations

[13]. However, none of the multi-targeted approaches yielded significantly durable progression free outcome to date.

It is beginning to appear that the onset of cancer is a communal effort of assorted components, hence, treatment approach that can target the systemic corruption of including intra- and extra-cellular factors may require to end the oncogenic disarray in the systemic homeostasis, especially in the case of ovarian cancer. The FAK/Src pair not only relays extracellular cues but also interacts with a number of pathways associated with chemo-resistant disease, including PI3K/AKT, MAPK, and JAK/STAT signalling (Figure 1). Targeting ARMs will potentially broaden the horizon of combined treatment as it may not only override the environmental oncogenicity but may also normalise the aberrant intracellular signalling. It has been demonstrated that interrupting aberrant ECM-to-cell signals mediated by integrins may normalise cell behaviour and reverse tumour development [14]. Further, it was also suggested that the early development of ovarian cancer is dependent on potential tumour forming cells being b
t
a
t
S
w
a



.

Figure 1: Schematic illustration of FAK/Src Adhesion-related molecules (ARMs) intracellular interactions: The cartoon shows diverse interactions of Adhesion-associated tyrosine kinases (AATKs) with pathways involved in cancer cell progression.

CONTRIBUTION

Dr. Makhdoom Sarwar	Conceptualization, Original draft, review and editing
Associate Professor Peter Sykes	Conceptualization, review
Professor John Evans	Conceptualization, review.

FUNDING

The authors of this manuscript received no funding for this work.

REFERENCES

1. Gockley, A. *et al.* Outcomes of women with high-grade and low-grade advanced-stage serous epithelial ovarian cancer. *Obstet. Gynecol.* **129**, 439–447 (2017).
2. Visvanathan, K. *et al.* Diagnosis of serous tubal intraepithelial carcinoma based on morphologic and immunohistochemical features: A reproducibility study. *Am. J. Surg. Pathol.* **35**, 1766–1775 (2011).
3. Labidi-Galy, S. I. *et al.* High grade serous ovarian carcinomas originate in the fallopian tube. *Nat. Commun.* **8**, 1–10 (2017).
4. Vaughan, S. *et al.* Rethinking ovarian cancer: Recommendations for improving outcomes. *Nat. Rev. Cancer* **11**, 719–725 (2011).
5. Prat, J., D'Angelo, E. & Espinosa, I. Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics. *Hum. Pathol.* **80**, 11–27 (2018).
6. Chitcholtan, K., Sykes, P. H. & Evans, J. J. The resistance of intracellular mediators to doxorubicin and cisplatin are distinct in 3D and 2D endometrial cancer. *J. Transl. Med.* **10**, 38 (2012).
7. Stone, R. L. *et al.* Focal adhesion kinase: An alternative focus for anti-angiogenesis therapy in ovarian cancer. *Cancer Biol. Ther.* **15**, 919–929 (2014).
8. Wiener, J. R. *et al.* Activated Src protein tyrosine kinase is overexpressed in late-stage human ovarian cancers. *Gynecol. Oncol.* **88**, 73–79 (2003).

9. Brasseur, K., Gévry, N. & Asselin, E. Chemoresistance and targeted therapies in ovarian and endometrial cancers. *Oncotarget* **8**, 4008–4042 (2017).

10. Liu, C. *et al.* The interaction between cancer stem cell marker CD133 and Src protein promotes Focal Adhesion Kinase (FAK) phosphorylation and cell migration. *J. Biol. Chem.* **291**, 15540–15550 (2016).

11. Schilder, R. J. *et al.* Phase II evaluation of dasatinib in the treatment of recurrent or persistent epithelial ovarian or primary peritoneal carcinoma: A gynecologic oncology group study. *Gynecol. Oncol.* **127**, 70–74 (2012).

12. Chen, T., Pengetnze, Y. & Taylor, C. C. Src inhibition enhances paclitaxel cytotoxicity in ovarian cancer cells by caspase-9-independent activation of caspase-3. *Mol. Cancer Ther.* **4**, 217–24 (2005).

13. Vetter, M. H. & Hays, J. L. Use of Targeted Therapeutics in Epithelial Ovarian Cancer: A Review of Current Literature and Future Directions. *Clin. Ther.* **40**, 361–371 (2018).

14. Weaver, V. M. *et al.* Reversion of the malignant phenotype of human breast cells in three- dimensional culture and in vivo by integrin blocking antibodies. *J. Cell Biol.* **137**, 231–245 (1997).

15. Evans, J. J., Alkaisi, M. M. & Sykes, P. H. Tumour Initiation: a Discussion on Evidence for a “Load-Trigger” Mechanism. *Cell Biochem. Biophys.* **77**, 293–308 (2019).

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 6 Jun 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: Associate Editor | **Revision** (1) 21 Jun 2020

Dear EIC,
This manuscript can be considered as an accepted article in the IJCM journal.
thank you

REFEREE: EIC | **Revision** (1) 21 Jun 2020

Dear author,
Please add the ORCID id of at least the first and corresponding authors in the authors' section. You can get an ORCID id from the ORCID website at https://orcid.org.
Thank you.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

CORRESPONDENCE:
A doctrine of ovarian cancer translational research needs revisiting.

Makhdoom Sarwar[1], Peter Sykes[1], John J Evans[1]

[1]*Department of Obstetrics and Gynaecology, University of Otago, Christchurch, 2 Riccarton Avenue, Christchurch 8011, New Zealand;*

Dear Editor,

There is no provision I can see in your system to add ORCID after submission.

Here is the ORCID ID of corresponding author.

Makhdoom Sarwar ORCID ID: 0000-0003-0030-7785, which was added manually by your support person in the author's profile.

Warm regards,

Dr. Makhdoom Sarwar, PhD, MRSNZ
Postdoctoral Fellow I Marcia Barnes Research Fellow
Gynaecologic Oncology,
Department of Obstetrics & Gynaecology,
University of Otago,
Christchurch, New Zealand.
Cell: +64 22 0287026

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision** (2) 27 Jun 2020

Dear authors,

Thank you for revising your manuscript according to the reviewers' comments.

Thanks