TBIOMD 492:
Critical Reading

The Role of Notch3 and Wnt Signaling Pathways in Ovarian Cancer Chemoresistance and Their Potential as Therapeutic Targets

Cayla Hayes
Mentor: Dr. EC Cline

Objective

In this literature review, I examined the roles of the Wnt and Notch signaling pathways in the context of ovarian cancer chemoresistance. The focus was on comparing their functions in normal biological processes with their involvement in cancer. This review delved into the underlying mechanisms of these pathways, the implications for treatment, and potential therapeutic targets that could arise from a deeper understanding of their roles in ovarian cancer.

Introduction

Ovarian Cancer and Its Challenges

- Ovarian Cancer (OC) is one of the deadliest cancers that affect women, with a high mortality rate at 71% (Lawson-Michod et al. 2022).
- Its main contributor is late diagnosis, due to mistaken symptoms.
- Most common is Epithelial Ovarian Cancer (EOC), which has two subtypes: High-grade Serous Carcinoma (HGSC) and Low-grade Serous Carcinoma (LGSO).

Current Treatment

- Primary treatment includes chemotherapy and surgery.
- OC has a 70% likelihood of relapsing or becoming chemoresistant.
- Chemoresistance is defined as cancer progression within six months of platinum-based treatment.
- Platinum-based treatment is a type of cancer treatment that targets and damage cancer cells' DNA (Zhang et al. 2022).

Wingless-related Integrated Site (Wnt) Pathway

- Important for OC progression and chemoresistance when activated due to elevated levels of CD44v6 which increases aggression.
- Inhibiting the Wnt pathway by silencing or knocking out the ROR1 and ROR2 receptors reduces chemoresistance (Henry et al. 2015).

Notch3 Pathway

- Overexpression of Notch3 protein causes chemoresistance.
- Inhibitors helps increase expression on MiRNA-136.

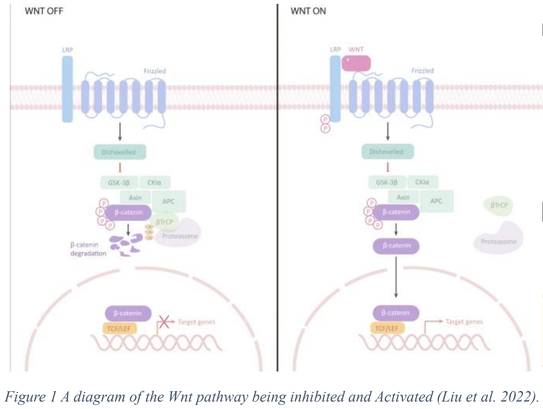

Figure 1 A diagram of the Wnt pathway being inhibited and Activated (Liu et al. 2022).

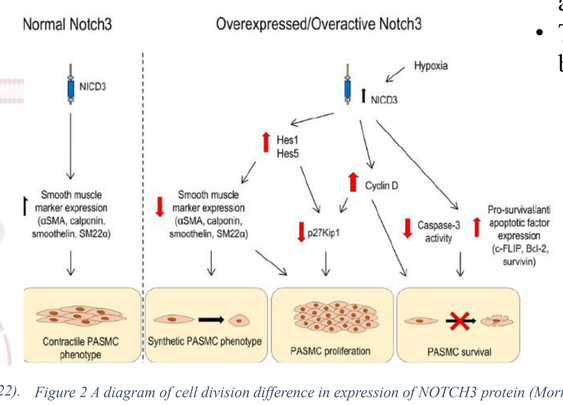

Figure 2 A diagram of cell division difference in expression of NOTCH3 protein (Morris et al 2019).

Inhibitors

PARP Inhibitors

- The PARP pathway plays a crucial role in the DNA repair process (Demény and Virág 2021).
- In cancer cells that develop resistance to chemotherapy, PARP inhibitors (PARPis) are employed to block the PARP enzyme, preventing the cancer cells from repairing themselves, ultimately leading to their death.
- The FDA has approved three PARPis for the treatment of ovarian cancer:
  - Olaparib
  - Niraparib
  - Rucaparib
- A study by Ji et al. (2025) compared these three FDA-approved PARPis.
- The study specifically examined their effectiveness in treating recurrent ovarian cancer.

RORs Inhibitor Effect on Wnt Pathway

- The Wnt signaling pathway plays a vital role in increasing the likelihood of tumor cells developing resistance to chemotherapy.
- Inhibiting this pathway may enhance the sensitivity of tumor cells to treatment.
- Silencing the receptors ROR1 and ROR2 significantly reduced tumor migration and invasion (Henry et al. 2015).
- When the researchers used small interfering RNA (siRNA) to knock down ROR1 and ROR2, they found little to no effect on cell proliferation or adhesion. However, there was a marked decrease in cell migration (Henry et al. 2015).

Inhibition of Notch Pathway

- Studies involving OC cell lines have observed a significant increase in Notch3 signaling pathway enzyme activity (Feng et al. 2016).
- This suggests that notch3 plays a critical role in the progression of OC creating a challenge for treatment.
- Study researchers used DAPT, which is a potent gamma-secretase inhibitor (GSI), which disrupts Notch signaling (Feng et al. 2016).
- This is a critical discovery because DAPT not only damages Notch3 activity but also can trigger apoptosis in cancer cells.
- These findings offer a new potential therapeutic strategy for managing OC by modulating the Notch signaling pathway.

Results/ Conclusion

- OC is deadly due to late diagnosis.
- PARis are a new class of drugs that improve survival rates.
- They are effective for both breast and ovarian cancer as they target similar cellular functions.
- The discovery of new therapeutic targets in the Wnt and Notch3 pathways offers promising new strategies to:
  - Hinder the growth and invasiveness of OC cells.
  - Improve the effectiveness of chemotherapy.

Future Directions

Addressing Chemoresistance

- Critical to understand the underlying cause of genetic mutations and biological pathways to better manage chemoresistance.
- Identifying these root causes can lead to personalized therapies that may restore a tumor sensitivity to chemotherapy.

Wnt and Notch3 pathway research

- The inhibition of the Wnt and Notch pathways has been shown promising in *in-vitro* studies (Chen et al., 2010).
- The next step is to conduct live organism trials to move closer to FDA approval for new treatments.

New Research

- Elevated glucose levels and metabolisms are significant indicators in cancer (Xintaropoulou et al. 2018).
- Targeting the glycolic process with inhibitors could be a promising future strategy as it would interfere with cancer cell growth.
- However, this approach may cause complications for individuals with metabolic disorders related to sugar conversion (Xintaropoulou et al. 2018).

New Medication

- Fuzuloparib has a strong possibility of being approved by the FDA as an OC maintenance therapeutic drug (Li et al. 2022).
- Its clinical trials in progression free survival (PFS) outcomes have been promising (Li et al. 2022).
- Already been approved in China for the treatment of platinum sensitive recurrent OC (Lee 2021).

Acknowledgement and References

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