Abstract

Ovarian cancer (OC) is the fifth leading cause of cancer-related deaths in women. However, ~70% of OC patients relapse and develop secondary resistance to therapy. Studies show that RAD6, an E2 ubiquitin-conjugating enzyme, is significantly overexpressed in ovarian tumors. Our data shows that RAD6 overexpression leads to an increase in DNA damage response proteins such as FANCD2, PCNA, RAD18, and γH2AX after carboplatin therapy. RAD6 upregulation also promotes increased expression of cancer stem cell signaling proteins ALDH1A1 and SOX2 in OC cell lines, which contributes to cancer recurrence and chemoresistance. Downregulation of RAD6 using siRNA or small molecule inhibitor T29 attenuated the expression of DNA damage response and stem cell signaling proteins, and results in re-sensitization of chemoresistant OC cell lines to carboplatin.

Hypothesis

1. RAD6 can be an important therapeutic target to prevent and treat acquired chemoresistance.
2. A RAD6 inhibitor, T29 can increase efficacy of available platinum based chemotherapeutic drug.

Results

Figure 2: RAD6 mediated expression of ALDH1A1 & SOX2 after chemotherapy and RAD6 is a poor prognostic marker in OC.

Figure 3: SMI of RAD6 (TZ9) induces DDR

Figure 4: RAD6i TZ9 synergizes carboplatin induced cytotoxicity.

Conclusions

- Rad6 level increases in response to chemotherapy.
- Inhibition of RAD6 attenuates HR-mediated DSB repair and PCNA mediated TLS pathway.
- RAD6 SMI TZ9 attenuates RAD6 mediated FANCD2 monoubiquitination.
- TZ9 sensitizes OC cells to carboplatin.
- Together, these results suggest that RAD6 attenuates DNA repair in OC and potential therapeutic target to prevent acquired chemoresistance in OC.

Future Directions

Future Goal of our lab is to identify and develop a novel secondary molecular inhibitor for RAD6 with better efficacy in human for treatment of acquired chemoresistant in ovarian cancer.

Acknowledgements

1. Texas Tech University Health Sciences Center.