Role of TRAF3 in B cell lymphoma susceptibility to pharmacological inhibitors

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BACKGROUND

- Out of the 242 billion cells our body produces a day, at least 1 million contain mutations, and thus have the potential to develop into cancer cells.
- As of 2012, 14.1 million people are diagnosed with cancer, and 8.2 million of these cases result in death (National Cancer Institute, 2016).
- We are studying a signaling protein called TNF Receptor Associated Factor 3 (TRAF3) that restrains survival of B lymphocytes, therefore keeping cells from overgrowth and mutations.
- TRAF3 regulates survival pathways, therefore preserving B cell homeostasis (Liao, Zhang, Harhaj, & Sun, 2004, pg 4).
- In humans, the loss of TRAF3 is found in certain cancers of B cells, such as multiple myeloma and lymphoma.
- Lymphoma is a cancer of B cells, the cells responsible for producing antibodies. (Smedby, Baeklund, & Askling, 2006, pg.11).
- Many of the chemical inhibitors used in treating lymphoma work by blocking signaling pathways required for cell survival, and therefore inhibiting the tumor cells from proliferation (Zahreddine & Borden, 2013, pg.5).
- Since TRAF3 is an important regulator of these signaling pathways, it is imperative to study the impact of pharmacological chemical inhibitors on B lymphoma cells in the absence of TRAF3.
- In the absence of TRAF3 to inhibit cell survival pathways, cells take advantage of the deficiency with abnormally enhanced survival.
- Knowing which TRAF3-regulated survival pathways can be inhibited by available drugs can better inform treatment of patients with TRAF3-deficient B cell cancers.

HOW WE DID IT

Our lab group cultivated different human lymphoma cell lines. We focused on 4 of them:

1) BJAB (TRAF3 Sufficient)
2) OCI-Ly7 (TRAF3 Deficient)
3) RAMOS (Small amount of TRAF3)
4) RAMOS-2g6 (Small amount of TRAF3)

We then applied two different drugs, Tivantinib and SGI 1776, in various concentrations. We then measured the cell death with a flow cytometer.

RESULTS

- The BJAB cell line (TRAF3 sufficient) had a significantly higher survival rate against both Tivantinib and SGI 1776 than the other cell lines.
- Ramos and Ramos 2g6 were fairly affected by the drugs.
- OCI Ly7 (TRAF3 Deficient) experienced the most cell death.

CONCLUSION

- When TRAF3 is lost, lymphoma cancer cells are more susceptible to certain biochemical inhibitors.
- Scientist can use TRAF3 deficiency as a window to target the vulnerable lymphoma cells with drugs.

Therefore, new questions arise.

- How can we identify TRAF3 deficiency in human lymphoma cells?
- How can we bypass the normal function of TRAF3 for the chemical inhibitor to work better in killing lymphoma cells?
- Why are the cancer cells more susceptible to chemical inhibitors where TRAF3 is absent?

Our study points out the significance of TRAF3 in how lymphoma cells respond to chemical inhibitors. Future studies will determine how specific inhibitors of TRAF3-regulated pathways can most effectively target survival of TRAF3-deficient malignant B cells.

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Figure 1: TRAF3 and CD40 Signaling

Figure 5: Flow Cytometer readings for 2.5 uM concentration SGI-1776: Left (BJAB) is high survival, Right (OCI Ly7) is low survival

Figure 2: Blots showing the amount of TRAF3 in different cell lines. Picture: Gail Bishop Lab—7/11/16

Figure 6: Graph of percent survival against the different concentrations of Tivantinib.

Figure 7: Graph of percent survival against the different concentrations of SGI-1776.

Figure 3: Graph of percent survival against the different concentrations of Tivantinib.

Figure 4: Graph of percent survival against the different concentrations of SGI-1776.

Figure 8: Flow Cytometer readings for 2.5 uM concentration SGI-1776.