Investigating BCL-2 Family Regulated Apoptosis in B-Cell Lymphoma

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Background and Aims

- The BCL-2 family consists of apoptotic and anti-apoptotic proteins and their equilibrium is an important factor in regulating cell death.
- Apoptosis is the process of programmed cell death and is vital for cancer therapy. Cancers such as B-Cell Lymphoma can avoid apoptosis and sustain malignant cells.
- In B-Cell Lymphoma, either anti-apoptotic proteins are over-expressed or pro-apoptotic proteins are under-expressed.
- Decreasing the presence of anti-apoptotic BCL-2 family proteins such as MCL-1 can inhibit lymphomagenesis. Lymphomagenesis refers to the growth of lymphoma and is aided by anti-apoptotic proteins.
- Lymphomagenesis can be prevented and delayed when the anti-apoptotic BCL-2 protein is inhibited by the BH3 mimetic ABT-737. ABT-737 is a BH3 mimetic drug that inhibits BCL-xl, BCL-2, and BCL-w all of which are anti-apoptotic BCL-2 family proteins.
- Understanding the interactions of the BCL-2 family in apoptosis is crucial to help develop various cancer therapies.
- The aim of this study is to examine how the BCL-2 family can prevent lymphomagenesis and promote apoptosis amongst malignant B-Cells.
- Literature pertaining to BCL-2 family regulated apoptosis was reviewed using databases on PubMed and Google Scholar and the data was examined to prove its efficacy in treating B-Cell lymphoma.
- The studies in the databases were conducted within the last 10 years to maintain relevancy and accuracy.
- The data collected from the studies can help in understanding the effects of inhibiting anti-apoptotic BCL-2 family proteins on B-Cell tumor development.

Figures and Results

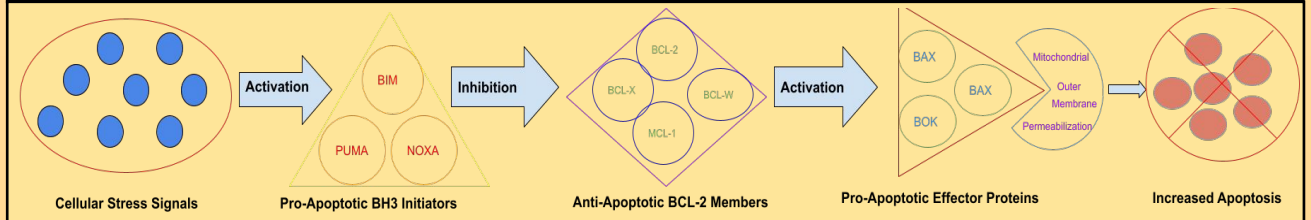


Figure 1: The BCL-2 protein family are key regulators of apoptosis. When the pro-apoptotic BH3 initiators are activated from stress signals through the mitochondria, the proteins inhibit the anti-apoptotic BCL-2 family proteins. The process leads to the activation of pro-apoptotic effectors resulting in Mitochondrial Outer Membrane Permeabilization (MOMP). MOMP is a cellular process which makes the cell permeable to proteins allowing programmed cell death or apoptosis to occur. Inhibiting anti-apoptotic BCL-2 family proteins is crucial to apoptosis and tumor-free survival.

Figure 2: (Grabow S, Delbridge AR, Aubrey BJ, Vandenberg CJ, Strasser, 2016)
Eμ-Myc mice (control) and Eμ-Myc;Mcl-$1^{+/-}$ mice with reduced MCL-1 levels were studied based on their rate of B-Cell Lymphoma development for a period of 800 days. The Eμ-Myc mice completely developed B-Cell Lymphoma in approximately 200 days whereas greater than 80% of the Eμ-Myc;Mcl-1+/− were lymphoma free. The reduction of MCL-1 protein levels delayed the lymphoma development until it was stagnant at around 500-800 days in where approximately 61 percent of Eμ-Myc;Mcl-1+/− mice were tumor free.

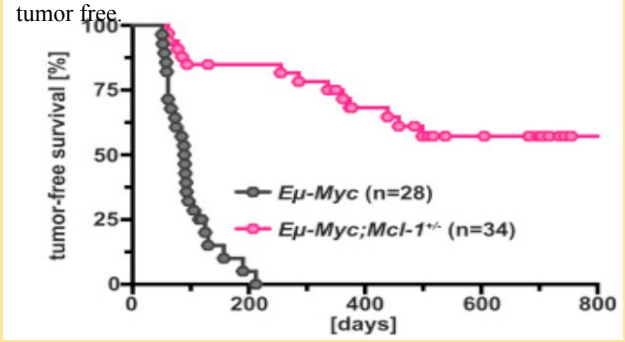
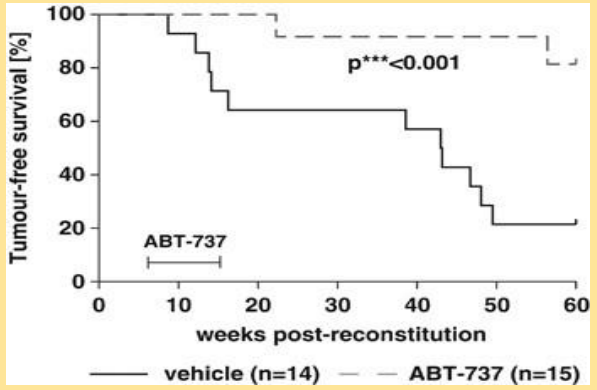


Figure 3: (Kelly, P., Grabow, S., Delbridge, 2013)
Eμ-Myc mice were injected with 75 mg of ABT-737 3 times a week for 8 weeks. ABT-737 is a BH3 mimetic that inhibits BCL-xl, BCL-2, and BCL-w. B-Cell Lymphoma development was then monitored over a period of 60 weeks. ABT-737 injections delayed lymphoma development until around 22 weeks in. At the end of the trial, 80% of ABT-737 treated Eμ-Myc mice were tumor free whereas only 20% of the vehicle control were tumor free.



Conclusion

The BCL-2 protein family is both diverse in its apoptotic stance and its capabilities during cancer treatment. Understanding the regulation of the BCL-2 family proteins is crucial to fighting cancer. The data presented showed that inhibiting the anti-apoptotic BCL-2 proteins effectively limited lymphomagenesis. Furthermore, various cancer treatments such as ABT-737 injections can be introduced on a larger scale in the oncological field. However, it is important to know that reactions by Eμ-Myc mice do not perfectly correlate to human beings.

Future Directions

The next step should be to investigate the effects of reducing MCL-1 levels or injecting ABT-737 in human beings to understand its efficacy for cancer therapy use. Further research can be conducted to understand the role of pro-apoptotic BCL-2 members on regulating programmed cell death in cancerous tumors. Recognizing the most effective BCL-2 member in limiting lymphomagenesis and examining interactions between BCL-2 members can bolster efforts to develop effective cancer therapies.

References

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