Targeting GLI3 in Diffuse Large B-cell Lymphoma

The goal of my project was to examine the potential role of GLI3 transcription factor in the different subtypes of Diffuse Large B-cell Lymphoma (DLBCL), with the ultimate goal of helping improve cancer treatment. DLBCL is a common type of non-Hodgkin's lymphoma, a cancer that develops in the immune system. DLBCL can be further subdivided into activated B-cell (ABC) like and germinal center B-cell (GCB) like subtypes. Each of these shows distinct features that correlate with the expression of target genes. Along with the factors affecting the subtypes, GLI proteins, which are members of the hedgehog signaling (Hh) pathway are very important when it comes to genes in this cancer (Singh et al., 2011). GLI proteins are important in the transcription factors of these genes because they regulate target gene expression by directly binding to their specific sequences (binding sites) in the promoter regions of these target genes (Young Ok et al., n.d.). Hedgehog (Hh) signaling pathway is very important in embryonic development, tissue patterning and maintenance of stem cells in adult tissue (Young Ok et al., n.d.). Improper Hh pathway signaling takes place in many cancers including DLBCL. Incorrect activation of the pathway has effects on GLI stability. We proposed that GLI3 proteins affect the two subtypes and in order to understand the subtypes, the expression of GLI3 needed to be studied.

A bioinformatic analysis of GLI1-3 expression in DLBCL patient samples using publicly available databases was performed. We found a higher GLI3 expression in the GCB subtype than the ABC subtype. Furthermore, we performed knockdown experiments to examine the effect of gene knockdown on cell proliferation. We observed a decrease in cell proliferation in DOHH2 (GCB subtype) cell line and this corresponds to a reduction in GLI3 mRNA expression. A reduction in GLI3 mRNA expression was also found in the RIVA (ABC subtype) cell line, however it did not correlate with a decrease in cell proliferation. These observations suggest that

GLI3 plays a role in GCB DLBCL growth and its knockdown may provide therapeutic benefit for GCB DLBCL patients. In addition to GLI3 knockdown, these cell lines were also treated with two drugs, dexamethasone and doxorubicin. Treatment with both of these drugs, in combination with GLI3 knockdown, did not result in a decrease of cell proliferation in either subtype. However, future studies will be testing new drug concentrations.

My objective was to examine the potential role of GLI3 transcription factors in the subtypes of DLBCL. I was able to see the effect knockdown had on cell proliferation in both subtypes, as well as the effect it had in combination with drug treatment. I was able to accomplish these objectives, however, the treatment with drugs is still in progress. Future studies will test different drug concentrations for drugs previously used, as well as new drug therapies.

Student Engagement Fund has allowed me to continue researching, which is allowing me get one step closer to my career goals. It has helped me develop professionally and academically. Professionally, my research has allowed me to present at various conferences outside of NIU. It has also allowed me to learn lab techniques that I will be able to use in the future. Academically, research has helped me reinforce what I learn in the classroom through hands on experiments.

References

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