Targeting NF-κB Signaling using a Novel Inhibitor in DLBCL

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Abstract

• Diffuse large B-cell lymphoma (DLBCL) is an aggressive B-cell malignancy that can be categorized by cell of origin, molecular features and reoccurring mutations.
• The transcription factor “NF-κB” plays a key role in cell survival, inflammation and immune responses; in cancer it promotes malignant cell proliferation.
• Targeting pathways such as the NF-κB is a viable option to treat B-cell malignancies.
• A novel NF-κB inhibitor was evaluated in DLBCL cell lines (OCI-LY3, RI-1, and Pfeiffer).
• The NF-κB inhibitor showed cytotoxic effects in DLBCL cells, especially those dependent on NF-κB.

NF-κB-i decreased DLBCL cell proliferation especially for the ABC cell lines with the RI-1 cell line having the lowest IC50.

ABC-DLBCL cell lines are more dependent on NF-kB signaling compared to GBC which may be the reason why our novel NF-κB-i had a greater anti-proliferative effects (~2-6 folds).

This approach may be promising to treat DLBCL, especially more aggressive subtype.

Future studies are needed to validate the drugs mechanism of action and preclinical efficacy.

Methodology

Cell Proliferation Assay

• MTS assay is a colorimetric method used to determine the number of viable cells in proliferation using a tetrazolium salt (MTS).
• Cells that are metabolically active will convert the MTS salt into a purple formazan product.
• The amount of formazan measured at 490 nm absorbance is directly proportional to the number of living/proliferating cells.
• To determine half maximal inhibitory concentration (IC50) of drug-of-interest, cells are treated with various amounts of drug/inhibitor starting from high concentration to low (i.e., serial dilution).
• After drug treatment, the MTS salt solution is added, and absorbance is measured on a plate reader 3-4 hours later.

To evaluate the effects of our novel NF-κB inhibitor (NF-κB-i), GBC- and ABC-DLBCL cell lines were treated with NF-κB-i for 72 hours and cell proliferation was measured by MTS assay.

Results

MTS Proliferation Assay (72 h)

- Experiments repeated 3 times per cell line.
- Dotted line represents IC50 value.

Conclusion and Future Directions

NF-κB-i decreased DLBCL cell proliferation especially for the ABC cell lines with the RI-1 cell line having the lowest IC50.

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Introduction

DLBCL

• DLBCL is the most common type of non-Hodgkin lymphoma in adults, with an annual incidence > 25,000 cases.
• Patients have enlarged lymph nodes in the neck, groin, or abdomen with abundant infiltrating B-cells.
• The most common treatment is chemoimmunotherapy such as R-CHOP, which has a 5-year survival rate of 58%.
• DLBCL is clinically heterogeneous in part due to the diversity in gene expression and/or molecular features.
• Based on cell of origin, there are two prominent subtypes of DLBCL (85% of cases): germinal center B-cell “GBC-DLBCL” and activated B-cell “ABC-DLBCL”.
• These subtypes have distinct gene signatures/molecular patterns indicating different stages of B-cell differentiation and activation.
• ABC-DLBCL are characterized with active B-cell receptor-dependent NF-κB signaling.
• These molecular differences between GBC and ABC-DLBCL subtypes translate to clinical differences, with ABC-DLBCL having a poorer therapeutic outcome.

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References