Genetic expression profile analysis reveals Over-expression of CHEK1 and BRCA1 in High-Grade Follicular Lymphoma relative to Low-Grade Follicular Lymphoma

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Background

Follicular lymphoma (FL) is the second most frequent non-Hodgkin B cell lymphoma. Progressive genomic aberrations drive the progression of FL between low grade; high grade or transformation to Diffuse Large B Cell Lymphoma (DLBCL). FL are difficult to treat, and relapses are common. Novel therapies such as monoclonal antibodies, immuno-modulating drugs, and target therapy have recently been developed and approved for relapsed FL, however, multifaceted approach to develop effective therapies is needed.

DNA damage response (DDR) resulting from genetic abnormalities is well known in solid tumors but DDR activity in lymphoma is sketchy. Heightened DDR can compromise therapeutic efficacy of DNA damaging drugs. Inhibitors of DNA repair molecules are providing clinical benefits as adjuvants in solid tumours (synthetic lethality). This study investigated the distinct gene expression pattern (GEP) for DDR molecules in a series of low- and high-grade FL as well as in DLBCL. Our findings will pave the pathway for adoption of synthetic lethality in lymphoma therapies, and hence carries promise to improve clinical outcomes in FL patients.

Methods

Diagnostic FFPE RNA from 98 FL and 27 DLBCL patient samples were screened for genes implicated with carcinogenesis, tumor microenvironment and immune response (n = 760) via PanCancer IO360 platform (Nanostring Technologies). Patients were categorized into high-grade FL (n = 22) FL and low-grade FL (n = 76). Gene Set Enrichment Analysis (GSEA) was performed for further correlation utilizing public data sets ($p < 0.05$, $q < 0.1$) using the titular GSEA software (v4.1.0, Broad Institute inc.).

Results

BRCA1 and CHEK1 were differentially expressed DDR response genes in late-grade FL relative to early-grade FL (figure 1A). CHEK1, an enzyme which facilitates the DDR in the cell cycle checkpoint arrest, was differentially expressed in these tumors alongside the tumor suppressor gene BRCA1, which conducts double stranded break repair (figure 1B). More DDR effectors were up-regulated in DLBCL compared to higher-grade lymphomas, suggesting CHEK1 inhibition could sensitize high-grade FL to therapies (figure 1C).

Conclusion

Our data indicate that DDR molecules are over expressed in high grade FL as well as in DLBCL, when compared with low grade FL. This enhanced DDR expression is likely to cause resistance to conventional therapies among high grade FL. These observations indicate that specific inhibitors like CHECK1/ BRCA1 and WEE1 can be explored as adjuvant therapeutic agent in high grade FL and DLBCL.