Genomic Landscape of Reed-Sternberg Cells of Hodgkin Lymphoma from Children, Adolescents, and Young Adults

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Introduction

Genomic evaluation of classical Hodgkin lymphoma (cHL) is challenging due to the scarcity of Hodgkin and Reed-Sternberg (HRS) cells within an extensive reactive microenvironment. To overcome this limitation our group has optimized flow-sorting to isolate HRS cells followed by exome sequencing using ultra low input DNA (Reichel et al, Blood 2015). This approach has been used to describe the exome of 10 cHL biopsies, most of which were from adult patients. To better understand the mutational landscape of cHL in children, adolescents and young adults, we performed whole exome sequencing (WES) on 54 cases and whole genome sequencing (WGS) on 9 cases.

Methods

HRS cells and intra-tumoral T-cells were isolated from cHL biopsies as previously described (Reichel at al, Blood 2015). Library construction was performed using the Kapa Hyper Plus Kit (Roche). A portion of library constructs were used for WGS; the remaining libraries were captured/amplified using SeqCap EZ Human Exome v3.0 probes (Roche) for WES. Exomes were analyzed using the MC3 pipeline. Somatic copy number analysis was performed using TITAN.

Results

WES was performed on 54 cases: 42 from children/AYAs (age 0-39yrs) and 12 from older adults (age ³40yrs). Histology included nodular sclerosis (83%), mixed cellularity (13%) and lymphocyte rich (4%). EBV was positive in 18%. For WES, the mean coverage was 80x for tumor and 48x for germline; the mean tumor purity was 61%. The average tumor mutation burdern was 5.9 mutations/MB. A total of 46,635 variants across 14,579 genes were found including 2,194 indels and 16,909 misense mutations. The most common non-silent alterations were *SOCS1* (61%), *SYNE1* (39%), *DNHD1* (37%), *TNFAIP3* (37%), *B2M* (33%), *OTOG* (30%), *ITPKB* (28%), *RYR2* (28%), and *DNAH9* (26%). Recurrent copy number gains and losses were detected, including the *B2M* locus. WGS was performed on 9 cases with mean coverage of 71x in tumor and 34x in germline. Analysis of structural variants is ongoing and will be presented.

Conclusion

Here we present the largest cohort of cHL to be analyzed by WES and the first WGS. The most common gene alteration was in *SOCS1*, which is also the most common alteration reported in primary mediastinal B-cell lymphoma (Mottok et al, Blood 2019). Additional alterations in cHL, however, suggest a unique

molecular signature. This work highlights the genomic diversity of cHL, potential differences across the age spectrum, and opportunities to explore novel therapeutic targets.

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