Comparative analyses of cranial and extra-cranial rhabdoid tumours reveal subgroups with cytotoxic T cell infiltration

Hye-Jung E. Chun[1], Pascal D. Johann, Katy Milne, Marc Zapatka, Annette Buellesbach, Naveed Ishaque, Murat Iskar, Serap Erkek, Lisa Wei, Basile Tessier-Cloutier, Jake Lever, Emma Titmuss, James Topham, Reanne Bowlby, Eric Chuah, Karen L. Mungall, Yussanne Ma, Andrew J. Mungall, Richard A. Moore, Michael D. Taylor, Daniela S. Gerhard, Steven J.M. Jones, Andrey Korshunov, Manfred Gessler, Kornelius Kerl, Martin Hasselblatt, Michael C. Frühwald, Elizabeth J. Perlman, Brad H. Nelson, Stefan M. Pfister, Marcel Kool, Marco A. Marra.

[1]Canada's Michael Smith Genome Sciences Centre, BC Cancer

Rhabdoid tumours (RTs) are highly aggressive paediatric cancers that predominantly affect infants, without established treatments to date. RTs exhibit pathognomonic loss of SMARCB1, a subunit of the SWI/SNF chromatin-remodelling complex that plays important roles in epigenetic and gene expression regulation. RTs arise from diverse anatomical sites, and based on these, they have been broadly classified into cranial atypical teratoid RTs (ATRTs) and extra-cranial malignant RTs (MRTs). Previous studies investigated ATRTs and MRTs separately, and reported multiple gene expression and DNA methylation subgroups within each entity. Although observations from these studies indicated some molecular features shared between ATRTs and MRTs, there had been no direct comparison made to determine biological connections between them. Furthermore, genomic, gene expression and epigenetic similarities and differences across RTs from multiple anatomical sites had not been comprehensively characterized, limiting our understanding of overall RT pathobiology, and our ability to refine its classification and reveal therapeutic implications associated with such classification. To address these limitations, we consolidated multi-omic datasets derived from 161 ATRTs and 140 MRTs, and performed integrative meta-data analyses. We found that the MYC-over-expressing subgroup of ATRTs (ATRT-MYC) and MRTs were similar at gene expression and epigenetic levels compared to other ATRT subgroups. Molecular features shared between ATRT-MYC and MRTs included *HOX* over-expression, particularly driven by a super-enhancer at the *HOXC* locus, global DNA hypomethylation and mesenchymal-like gene expression profiles, which distinguished ATRT-MYC and MRTs from other ATRT subgroups that exhibited neural-like gene expression profiles. Our work further determined five DNA methylation subgroups of RTs across different anatomical sites, namely "ATRT-MYC-like" Group 1, "ATRT-TYR-like" Group 2, "Renal MRT-like" Group 3, "Extra-renal MRT-like" Group 4 and "ATRT-SHH-like" Group 5. Importantly, our work showed that subgroups consisting of ATRT-MYC and MRT cases, i.e. Groups 1, 3 and 4, exhibited gene expression signatures and epigenetic modifications indicative of increased immunogenicity compared to other RT subgroups. Gene expression analyses further showed increased expression of immune checkpoint genes in RT cases that were predicted to have increased T cell infiltration, while cases predicted to have low T cell infiltration exhibited decreased expression of genes involved in antigen processing and presentation, suggesting mechanisms of immune evasion. We confirmed increased levels of cytotoxic T cell and PD-L1-expressing macrophage infiltration in Groups 1, 3 and 4 using multiplex immunohistochemistry. Our findings implicate a potential role of immunotherapy in the context of RTs, despite the very low prevalence of mutations in this paediatric cancer.