PL4

The Molecular Landscape of Malignant Peripheral Nerve Sheath Tumour (MPNST)

Lindsay, D.[1]; Hookway, E.[2]; Steele, C.[2]; Lombard, P.[2]; Gupta, M.[2]; Amary, F.[1]; Tirabosco, R.[1]; Ye, H.[1]; Strobl, A.[1]; Pillay, N.[2]; Flanagan, A.M.[2]

[1]Royal National Orthopaedic Hospital, London, United Kingdom; [2]University College London, London, United Kingdom

Purpose of the study: MPNST is a rare aggressive soft tissue sarcoma. In 45% of patients it is associated with Neurofibromatosis type-1 caused by germline mutations in *NF1*: 45% occur in a sporadic setting, and 10% are radiation-induced. This study takes an integrated approach to the analyses of the heritable/somatic mutational landscape, and methylomes of 46 MPNSTs.

Methods: Whole exome sequencing was undertaken on 46 MPNSTs with matched normal tissue. A total of 67 MPNSTs were analysed on the 450K Illumina methylation array, and compared with the methylation profiles of 67 undifferentiated sarcomas (USARC) and 170 soft tissue tumours from an independent cohort. t-Stochastic Neighbour Embedding (t-SNE) analysis was undertaken to assess how closely these tumours are related at an epigenetic level.

Summary of results: 18 tumours showed bi-allelic somatic alterations in *NF1* and an additional 14 patients had germline mutations in *NF1*. Whole genome sequencing would be required for complete assessment of *NF1* alterations. Epigenetically, MPNST formed three distinct clusters; cluster 1 overlapped with USARC, and the second only contained paraspinal MPNST. Cluster 3 showed loss of expression H3K27me3 (a marker of Polycomb Repressive Complex 2 (PRC-2) activity) on immunohistochemistry. The genomic loci in cluster 3, which represent those that are normally subject to repression by an intact PRC-2, are significantly hypermethylated compared to those in cluster 1. Patients in cluster 3 had a shorter survival than those in cluster 1 ($p=0.00085$).

Conclusions: We have identified 2 groups of MPNST defined by their DNA methylation profiles which provides prognostic information for patients with this disease. It also demonstrates that DNA sequencing provides more accurate diagnostic classification of soft tissue sarcomas.