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Needle in a haystack: identifying drivers of malignant transformation in neurofibromas

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See the article by Pemov et al. in this issue, pp. 981-992.

In the setting of neurofibromatosis type 1 (NF1), an autosomal dominant tumor predisposition syndrome, the early identification of malignant peripheral nerve sheath tumors (MPNSTs) poses a major clinical challenge. Individuals with NF1 develop innumerable peripheral nerve sheath tumors that arise from Schwann cells. Although the majority of these lesions are benign, there is a lifetime risk of 8–16% of malignant transformation in one of these lesions into an MPNST.[1] The prognosis for this aggressive sarcoma is poor, with a 5-year survival ranging 20–50%, and therapeutic options are limited.[2] Therefore, it is prudent to develop clinical and molecular biomarkers that identify tumors at risk of malignant transformation.

Pemov et al evaluated the molecular landscape of atypical neurofibromas, a histopathological variant of neurofibroma thought to be a premalignant lesion, with bulk tumor whole exome sequencing, whole transcriptome sequencing, single nucleotide polymorphism array, and immunohistochemistry.[3] Previous studies of MPNSTs had identified recurrent loss of *NF1*, cyclin-dependent kinase inhibitor 2A (*CDKN2A*), and polycomb repressive complex 2 (PRC2).[4,5,6] In contrast, neurofibromas only harbor *NF1* loss. Atypical neurofibromas have an additional deletion of chromosome 9p, encompassing the CDKN2A locus, which suggests that loss of CDKN2A is an early driver of malignant transformation.[3,7] However, it remains unclear what other molecular alterations and pathway dysregulation play a role in malignant transformation.

The authors demonstrate that atypical neurofibromas have low mutational burden and relatively stable chromosomal profile. *NF1* and *CDKN2A* alterations were identified in atypical neurofibromas. In addition, *SMARCA2* deletions were identified in 42% of atypical neurofibromas. Most importantly, for the first time, the authors identified a lack of *SUZ12* and *EED* alterations, which are components of PRC2, in atypical neurofibromas. Based on these findings, the authors conclude that deletion of *CDKN2A* primarily drives the transformation of neurofibromas to atypical neurofibromas.

The molecular findings further support the notion that premalignant neurofibromas are a separate tumor entity. On histopathology, these tumors harbor characteristics worrisome for malignant progression with increased cellularity, nuclear atypia, mitotic activity, or loss of neurofibroma architecture.[8] Currently, clinical data have not been established to completely characterize the risk of malignant transformation in these tumors, but the histopathological and molecular data suggest that *CDKN2A* loss is sufficient to progress to a premalignant phenotype but not enough for malignancy.

The results of this study and others[7] beg the question of what drives the malignant transformation of atypical neurofibromas into MPNSTs. A robust method of addressing this question would be to study the genomic profiles of premalignant neurofibromas and the corresponding matched MPNSTs to identify the molecular pathways driving malignant transformation. However, this approach may not be feasible due to current clinical practice patterns and the relative rarity of tumors undergoing malignant transformation after an initial debulking surgery. Alternatively, since MPNSTs are heterogeneous and parts of the tumor may retain the original underlying benign neurofibroma cells, multisampling of histologically distinct areas within a single MPNST may elucidate the sequence of genomic alterations leading to malignant transformation.

One major challenge in studying the molecular profile of neurofibromas is the presence of multiple cell types within the tumor. Neurofibromas are characterized by the presence of non-neoplastic cells, including axons, perineural cells, fibroblasts, and variable inflammatory elements.[9] A major difficulty in determining causative mutations in heterogeneous tumors such as neurofibromas and MPNSTs

is the combination of non-neoplastic cells and different tumor subclones, given that there is an accumulation of mutations during progression. Therefore, conventional bulk tumor whole exome sequencing and bioinformatic pipelines may not be powerful enough to detect low-allelic-fraction mutations.[10]

One way to circumvent the problem of mixed cell types in a tumor sample would be to harness single cell sequencing technology. Single cell whole exome and RNA sequencing have been important tools in studying tumoral heterogeneity and subclonal evolution in other cancers.[11] This study highlights the need for more sophisticated sequencing modalities to study the drivers of malignant transformation in neurofibromas and MPNSTs.

Conflict of interest statement. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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