EDITORIAL

DICER1-sarcoma: an emerging entity

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In this issue of *Modern Pathology*, Kommoss et al. report on the clinicopathological and molecular features of *DICER1*-mutant and *DICER1*-wild type embryonal rhabdomyosarcomas (ERMS) in a series of genitourinary tumours¹. The authors studied 17 ERMS, including 9 uterine (four corpus and five cervix), one vaginal and seven urinary tract tumours. They showed pathogenic variants (PVs) of *DICER1* in 9/9 uterine ERMS while all other ERMS were *DICER1*-wild type. The median age at diagnosis of patients with *DICER1*-mutant and *DICER1*-wild type ERMS was 36 and 5 years, respectively. Limited follow-up data suggested that *DICER1*-mutant tumours might exhibit a less aggressive clinical course than *DICER1*-wild type. Cartilaginous elements were only observed in *DICER1*-mutant ERMS (6/9 *DICER1*-mutant ERMS) and in one case this was accompanied by foci of ossification. Unsupervised hierarchical clustering of array-based whole-genome DNA methylation data of their series together with an extended methylation data set including different rhabdomyosarcoma (RMS) subtypes from genitourinary and extra-genitourinary locations ($n = 102$), revealed a distinct cluster for *DICER1*-mutant ERMS. These tumours clearly segregated from the clusters of *DICER1*-wild type ERMS, alveolar RMS and MYOD1-mutant spindle cell and sclerosing RMS. Only one tumour, an ERMS in the maxilla of a 6-year-old boy, clustered with *DICER1*-mutant ERMS of the uterus. Subsequent sequencing analysis of this case identified two *DICER1* PVs. The authors concluded that *DICER1*-mutant ERMS might represent a distinct subtype in the future classification of RMS.

This paper adds to a series of publications in the last decade^{2–9} that have shown a strong association between both germline and somatic PVs in *DICER1* in uterine ERMS, especially those arising in the cervix. As noted by the current authors¹, these tumours exhibit several characteristic features which can aid the pathologist in identifying a likely association with *DICER1* PVs¹⁰. Moreover, we and others^{11–13} have noted that many of these features, such as a subepithelial layer of malignant mesenchymal cells (cambium layer), areas of rhabdomyoblastic differentiation with positive staining with myogenin and myoD1, cellular/immature and occasionally malignant cartilage, foci of bone/osteoid and areas of anaplasia are shared by other sarcomas at different sites that possess either germline or somatic (or both) PVs in *DICER1*. Given the confusing proliferation of names for tumours that have similar appearances and a single genetic cause, we have argued for a simplified nomenclature of *DICER1*-related sarcomas, such that their tissue site and common molecular origins are recognised^{11,12}. For example, we suggest terms such as “primary peritoneal sarcoma, *DICER1*-mutant” and “primary cervical sarcoma, *DICER1*-mutant”.

DICER1 is part of the microRNA biogenesis pathway and perturbations in microRNAs underlie many developmental and neoplastic disorders. *DICER1* mutations have an unusual distribution in that in neoplasms, two hits are usually identified, but unlike most other genes that fit the “two-hit” hypothesis of tumour

formation, the hits are very different in nature; one hit is usually a protein-truncating loss-of-function variant, whereas the other specifically involves one of very few “hotspot” sites located in the critical RNase IIIb domain of *DICER1* protein¹⁴. This can facilitate simple genetic testing in the molecular pathology laboratory because if a hotspot is not found on targeted sequencing, it is unlikely that the tumour will be *DICER1*-related. This can be helpful for example in trying to distinguish uterine ERMS from adenocarcinoma, as the absence of a *DICER1* PV makes a diagnosis of ERMS very unlikely, although the presence of a PV does not help distinguish between the two tumours⁶. In other organ systems, this specificity has been exploited by commercial genomic assays such as Thyro-Seqv3¹⁵, which is helpful in management of patients with a thyroid nodule. The assay includes only the hotspot regions of *DICER1*, but because of the association of hotspot variants with second hits elsewhere in the gene, the assay can identify persons who may have germline *DICER1* PVs and hence *DICER1* syndrome¹⁶. Thus, genetic counselling should be offered to all persons found to have a hotspot PV in *DICER1*, unless a germline PV has already been excluded.

How else might this emerging class of tumours be more easily identified by pathologists? The paper by Kommoss et al.¹ suggests another intriguing possibility. The distinct cluster for *DICER1*-mutant ERMS mentioned above likely reflects the common tissue of origin or differentiation state of these tumours. While DNA methylation arrays may not be widely available in pathology laboratories, a minimalist approach has recently been suggested in this journal¹⁷ and could be applied in clinical diagnostic pathology laboratories. To generalise this approach, it will first have to be demonstrated that *DICER1*-sarcomas do indeed form a discrete, identifiable entity. Recently, a novel RMS-like methylation class referred to as “SARC” has been identified, which is populated by central nervous system (CNS) sarcomas with *DICER1* PVs¹⁸. *DICER1* may also be implicated in the related “SARC (malignant peripheral nerve sheath tumour (MPNST)-like)” methylation cluster, as a *DICER1* PV was reported in one of five MPNSTs¹⁹. While *DICER1*-related CNS sarcomas²⁰ will be unlikely to share a tissue of origin with sarcomas arising in the urogenital tract, there may be other *DICER1*-dictated events that lead to clustering. Intriguingly, there is a notable excess of females with *DICER1*-sarcomas and a possible link to the Müllerian system has been posited²¹. The strongest clue that this clustering may be generalisable, however, comes from the one outlier in the study of Kommoss et al.¹, mentioned above; this was a maxillary ERMS in a 6-year-old boy which was identified on the basis of the common clustering with truncating and hotspot *DICER1* mutations only discovered subsequently. Therefore, further methylation studies to determine whether *DICER1*-mutant sarcomas do indeed form a distinct, identifiable subgroup of sarcomas are warranted.

A recent review of the epigenomics of sarcoma²² suggests that many sarcomas can be viewed as epigenetic diseases with few, and sometime only one, mutation being required for their initiation. *DICER1* was not mentioned in this review, but in many ways *DICER1*-mutant sarcomas fit the bill for being predominantly

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an epigenetic disease and disruptions of the balance of microRNAs, and thus altered transcriptional programs, appear to be at the heart of the pathogenic process. Although *DICER1*-mutant sarcomas can contain additional genetic alterations in genes such as *NF1*, *RAS* or *TP53*^{1,23,24}, none appear to be obligatory for the specific pathologic features.

Identifying the common underlying biology could be critical not only for correctly classifying these unusual lesions, but also for developing rational therapies. The absence of any obligatory, targetable somatic variants in *DICER1*-mutant sarcomas poses significant challenges. Newer approaches, such as functional genomic screens using isogenic cell lines derived from patients with *DICER1*-mutated sarcomas, could prove to be a promising avenue.

In summary, unsupervised hierarchical clustering of array-based whole-genome methylation data of one subset of *DICER1*-mutant sarcomas has demonstrated that they cluster together. This finding should prompt further studies to clarify whether *DICER1*-mutant sarcomas are indeed a distinct identifiable subgroup of sarcomas.

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ADDITIONAL INFORMATION

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