CORRESPONDENCE

In Response to "Reexamining the molecular findings in specialized stromal tumors of the prostate"

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TO THE EDITOR:

We thank Dr. Pan and Dr. Epstein for their interest in our article "Reevaluating tumors of purported specialized prostatic stromal origin reveals molecular heterogeneity, including nonrecurring gene fusions characteristic of uterine and soft tissue sarcoma subtypes"[1,2]. In this study, based on the results of molecular analyses of a multi-institutional series of mesenchymal tumors of the prostate, we raised the possibility that so-called "stromal tumors of uncertain malignant potential" (STUMP) and "prostatic stromal sarcomas" (PSS) may not represent distinct biological entities. In our article we propose that, given this uncertainty, alternative diagnostic terms such as "mesenchymal tumor of uncertain malignant potential" and "unclassified low/intermediate/high-grade sarcoma" should be considered for mesenchymal tumors of the prostate that cannot be classified as more specific tumor types. We acknowledge that the evidence presented in our series is not definitive, and we do not irrevocably refute the idea that STUMP and PSS could represent specific entities. However, we believe that there are significant gaps in our understanding of these rare tumors that still need to be filled before a more definitive assertion can be made regarding their nature.

Thus far, from a molecular perspective, the only reported commonality among these tumors has been the presence of a few recurrent and overlapping chromosomal losses, including (but not restricted to) chromosomes 13 and 14[3,4]. Although defined patterns of chromosomal alterations may be characteristic of some entities, secondary recurrent chromosomal imbalances involving 1 or 2 chromosomes occur in a wide array of neoplasms and are mostly nonspecific. Across 10,967 samples from 32 cancer types in TCGA accessible through cbioportal, losses of chromosomes 13 and 14 are documented in 2272 of 8818 cases (20.7%), and in 1813 of 9100 cases (16.5%) for which copy number status is reported. Aneuploidy of chromosomes 13 and 14 are hence frequent chromosomal aberrations in cancer with very limited intrinsic diagnostic value[5].

Whole exome sequencing (WES) and array comparative genomic hybridization are robust techniques for copy number variant (CNV) detection but are suboptimal for detection of structural variants. Additionally, depending on the sequencing depth and sample quality, WES can have reduced sensitivity for single nucleotide variants (SNVs) relative to focused panel assays. In our series, close to 20% of tumors had clear evidence of a pathogenic gene fusion event (both gain of function and loss of function), arguing that assays that are optimized for gene fusion detection are essential for more complete molecular classification of mesenchymal neoplasms. Indeed, given the limitations of focused panel assays as used in our studies, this may be an underestimate. Importantly, many of the loss of function mutations detected in our study were associated with deletions or copy-neutral loss of heterozygosity, suggestive of biallelic inactivation of the affected genes and oncogenic dependence[1]. The new SNV findings presented in the letter from Pan et al. emphasize the critical importance of the informatics pipeline in either highlighting or filtering out potentially relevant variants and supports the need for dedicated validation of this pipeline when high complexity next generation sequencing assays are employed for clinical purposes. While it is certainly possible that single copy number deletions might be missed in samples with low tumor purity or high DNA degradation, our assay has proven to be reliable in validation studies and clinical practice for making CNV calls[6,7].

From a biological standpoint, the fact that variants are subclonal does not necessarily mean that they are irrelevant for oncogenesis. For example, it is possible that some of these mesenchymal lesions of the prostate consist of cellular stromal nodules in which a subpopulation of cells undergoes neoplastic transformation. Importantly, the observation that the authors make regarding the possible subclonal nature of the SNVs reported in our study can be similarly extrapolated to the chromosomal changes identified in their series. In fact, secondary recurrent chromosomal gains and losses have been described in multiple tumor types with concurrent well-known molecular drivers[8,9].

Three additional issues suggest that questioning the existence of STUMP and PSS as specific entities is not unjustified. Firstly, if one assumes that mesenchymal neoplasms with similar histomorphology and identical molecular drivers are biologically comparable, studies performed in recent years suggest that organ-specific mesenchymal tumors are exceptionally rare. Secondly, tumors classified as PSS and STUMP are morphologically diverse and lack specific adjunctive markers. Finally, it is somewhat uncertain whether the stromal cells of the prostate (and their neoplastic counterparts) represent a unique line of differentiation or phenotype that is different from myofibroblasts and fibroblasts of other structures derived from the mesoderm of the urogenital sinus.

We acknowledge that there might be inherent differences between the series analyzed by Pan et al.[3,4] and by our group[1]. For instance, our series had a higher proportion of PSS compared to their studies. Also, we used a multi-institutional approach (with centralized re-review) in an attempt to obtain a sample that was representative of the lesions that were diagnosed as PSS and STUMP by pathologists from different institutions. This design has the strength of better representing the universe of lesions classified as PSS and STUMP in the community. However, a multi-institutional series is potentially more heterogeneous than series diagnosed at one or two institutions.

In summary, we think that while PSS and STUMP have been useful diagnostic categories, it is valid to question their existence

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as specific, unified biologic entities in light of the evidence that is available presently. In this regard, cases diagnosed as STUMP and low-grade PSS could possibly span a spectrum from histologically worrisome but biologically indolent stromal nodules to true sarcomas. We currently believe that the existing data is still inconclusive and additional evidence is needed to clarify the nature of these rare mesenchymal neoplasms.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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