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Editorial

Diverse mutational signatures in endometrial cancer: implications for tumor etiology and evolution

The article by Ashley and colleagues [1] in this issue is a paper for the cancer genomics connoisseur. It builds upon the 2013 landmark study from the The Cancer Genome Atlas (TCGA) consortium [2] that was the first major multi-omics approach to molecularly characterize endometrial carcinomas and a more recent study of uterine carcinosarcomas by the same group [3]. The initial TCGA study focused on endometrioid and serous carcinomas (over-sampling high grade endometrioid and serous tumors). In combination with the subsequent analysis of carcinosarcomas, TCGA addressed what are among the most aggressive histologic subtypes of endometrial cancer.

An overarching goal for cancer genomics in general, and a point emphasized in the current paper, is that molecular signatures hold promise as prognostic markers, and more importantly as predictive markers. One good example of a predictive molecular marker for endometrial cancers is mismatch repair deficiency (evidenced by tumor MSI and/or immunohistochemistry) that is an eligibility criterion for immune checkpoint blockade therapy (pembrolizumab). The term genomics was first introduced in the mid-80s and in its earliest phases was unconcerned with function [4]. Today, genomics is a discipline that is technology and informatics driven and has ever-increasing resolution. Genomic studies now frequently have goals of understanding genomic function. The current paper addresses the mutational processes that *drive* endometrial tumor biology imputed from the analysis of individual tumors. The authors undertook a detailed evaluation of TCGA DNA sequencing results for primary tumors as well as a collection of matched primary and metastatic tumors [5].

TCGA defined four molecular subtypes of endometrial cancer and the associations of the molecular groups with patient outcomes. The four molecularly defined cancer subtypes are: POLE exonuclease domain mutation (POLE), microsatellite instable (MSI), microsatellite stable low copy-number alteration (MSS), and microsatellite stable high copy-number alteration (CNA, serous-like) (Fig. 1). Not surprisingly, carcinosarcomas were shown to have genomic profiles similar to those observed in endometrial carcinomas.

The analyses and report by Ashley and colleagues is a higher resolution endometrial cancer genomics study. Analyzing data from earlier studies using classification methods to assign "mutational signatures" [6] to tumors, they show that TCGA molecular classes are heterogeneous. It is not at all suprising that further "molecular phenotyping" would reveal additional complexity in endometrial cancers which are recognized as a histologically and biologically diverse cancer type (Fig. 1). As such, increased genomic resolution is expected to lead to further subclassification. The findings for endometrial cancers evaluated by methods with increasing resolution is reminiscent of the evolution of classification of hematologic malignancies based on cytologic features followed by cell surface markers, chromosomal abnormalities and more recently gene mutations. Importantly, mutational signatures speak to clinically relevant biological processes that drive tumor evolution. The clinical/therapeutic implications for mutation signatures are many see Ma et al. [7] for a recent review.

Many of the findings on endometrial cancer mutational signatures reported in this issue of *Gynecologic Oncology* are confirmatory and re-emphasize key and minor points made in earlier publications on endometrial and other cancer types. The methods used to further classify molecular subtypes of endometrial cancers were clearly effective. The current paper does, however, provide an important new view on tumor heterogeneity that comes from comparing mutational signatures in primary and metastatic tumors from the same patients. It has been shown previously that matched primary and metastatic tumors have different mutations. Ashley et al. have shown that the *processes* that determine the accumulation of tumor cell mutations (imputed from mutational signatures) differ between tumor sites (primary and separate metastases). The plasticity of cancer cells and tumor evolution has been made very clear through the study of endometrial cancers.

Some of the key findings from the current study include:

- Carcinosarcomas have similar mutational signatures as endometrial carcinomas, regardless of the relative fractions of sarcoma and carcinoma, indicating that the same mutational processes are at work.
- Dominant mutational signatures change as evidenced by analysis of primary and matched metastatic sites.
- Only a small fraction of endometrial cancers have a predominantly homologous repair deficient molecular signature. It should, however, be noted that the absence of such a signature in endometrial cancer does not prove that therapeutic approaches capitalizing on homologous repair deficiency in other tumor types will not be effective.

Mutational signatures for endometrial cancers as descried by Ashley et al. will lead to a series of debates on when to lump and when to split. ICD struggles with the question of when to lump and when to split. How gynecologic oncologists will interpret molecular classification and mutational signatures of endometrial cancers remains to be determined. Will molecular features trump tumor histology in the foreseeable future? The landmark TCGA classification of endometrial cancers in 2013 has influenced tumor board discussions, but to date has not dramatically changed patient care. Meanwhile, commercial tumor

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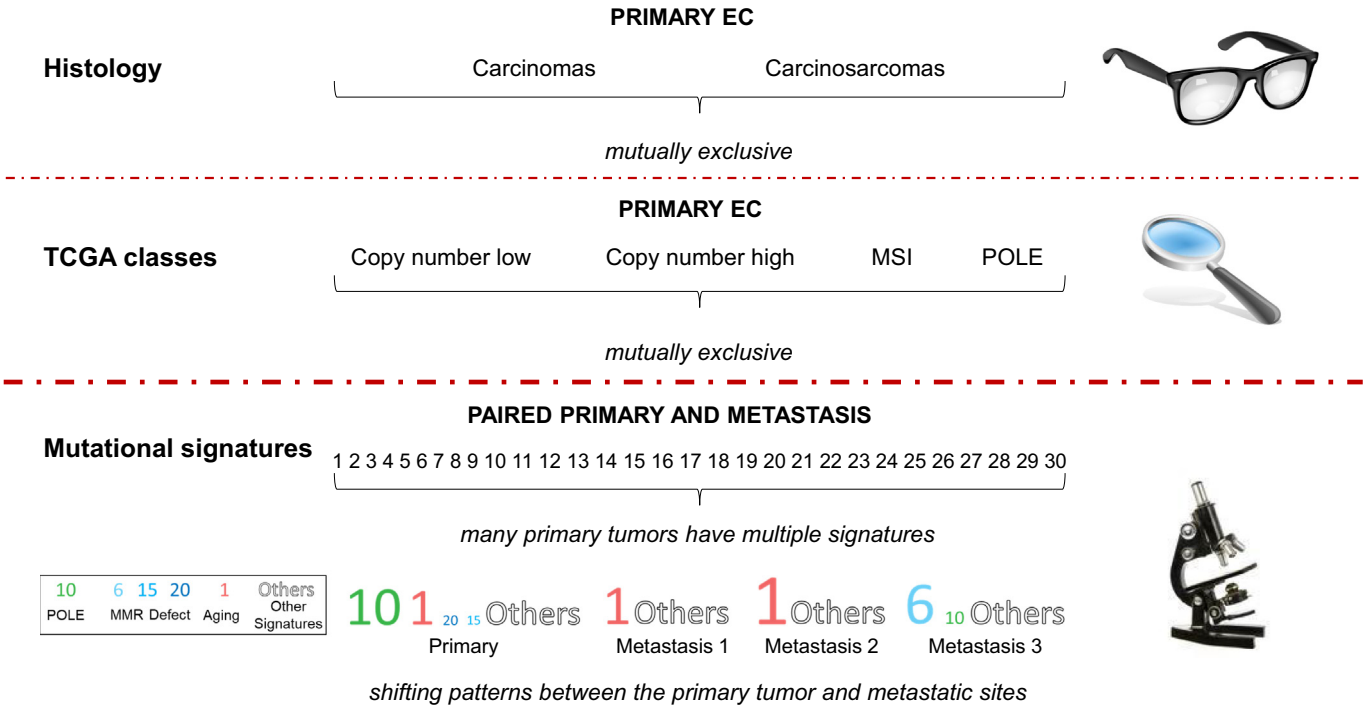

Fig. 1. Increasing resolution for characterizing endometrial cancers.

profiling has perhaps shaped how gynecologic oncologist make decisions about which clinical trials to consider for their patients.

How will the gynecologic oncology community gain insights into what the "best" predictive signatures are? This is a challenge given the small or modest numbers of patients receiving new therapies (as part of clinical trials or standard of care) and small fraction of such patients for whom tumor molecular profiling is performed. The depth of characterization required for molecular signatures (referring to not only the number of DNA sequence reads but also to how many different genes need to be interrogated) makes the findings here hard to generalize (read clinical applicability).

Perhaps the most important finding from the characterization of mutational signature is that sampling primary and metastatic lesions for genomic features at time of treatment will be essential to determining the best therapeutic options. An endometrial cancer patient with recurrent or persistent metastatic disease may actually have several tumor subtypes for which best treatments differ. The primary tumor may not demonstrate some features that were expanded as the tumor metastasized, such as mismatch repair or homologous repair deficiency.

And what else can we learn from mutational signatures? By understanding what processes drive the formation of endometrial cancers it may one day be possible to target such processes as part of endometrial cancer prevention studies. Time will tell….

Conflict of interest

The authors have no conflicts of interest to declare.

Author contribution

Both authors contributed to the writing of the editorial.

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