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ASO Author Reflections: Transitioning from morphology to transcriptomics in capturing tumor biology

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Past

In the world of surgical oncology, it is said that biology is King and selection of cases is Queen (1). Capturing tumor biology has been challenging, as it is difficult to define accurately. Historically, tumor biology has been defined anatomically as clinical stage, based on the tumor size, lymph node metastases, and distant metastasis. With deeper understanding of tumor morphology, pathological findings, such as lymphovascular invasion (LVI), perineural invasion (PNI), and grade have been considered as surrogate markers of aggressive tumor biology. However, pathological analyses are limited by subjective morphological evaluation. In breast cancers, with better understanding of hormonal receptors (HRs) as well as human epidermal growth factor receptor 2 (HER2), immunohistochemistry (IHC) and Fluorescence in situ hybridization (FISH) assessments have added another modalities to capture tumor biology.

Compared to other cancer types, histological grade in breast cancer has demonstrated compelling evidence to predict tumor biology. Especially, Nottingham grading system, composed of three pathological findings; tubular formation, nuclear pleomorphism, and mitotic counts, is the most validated system and demonstrated least inter-observer variability

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among various grading systems. Thus, Nottingham histological grade is incorporated to a significant component of the tumor stating in the latest 8th edition of the AJCC Breast Cancer Staging system (2). However, subjectivity of morphological assessment still remains.

Present

In recent years, innovation in genomic sequencing technology and computational bioinformatics analysis has enabled researchers to dissect the tumor immune microenvironment (TIME) at the genomic level, promoting further understanding of immunogenomics (3). For instance, our group has recently found that anti-cancer immunity counterbalance aggressive tumor biology in breast cancer with high mutation rate (4). It is now possible to assess tumor biology and underlying immunogenicity in a more objective way using transcriptomic data from the tumor samples combined with computational biological approach (4–6).

Recently, our group elucidated the tumor biology of pathologically determined aggressive breast cancers using the transcriptome profile. With three large cohorts including RNA-Sequence data of 2876 patients, Nottingham Grade 3 breast cancers were found to have aggressive clinical and transcriptomic features as well as enhanced immunity in their TIME. Our results suggested that Grade 3 breast cancers may respond better to immunotherapy given underlying enhanced immunity (7). In another study, we found that pathologically determined LVI positive breast cancer was highly proliferative without any enhanced immunity (8). As demonstrated in these two studies, transcriptomic analyses with computational bioinformatics approach lead to deeper understanding of biology of the tumors with pathologically defined aggressive clinical features.

Future

Although DNA-sequencing, such as FoundationOne and OmniSeq, has been more widely and commonly used in the clinical setting, RNA-Sequence data may have improved utility as transcriptomes may represent the tumor biology better (9). With Next Generation Sequence (NGS) becoming widely available with reasonable expenses, RNA-Sequence data will be more accessible and computational algorithms will be more sophisticated; thus, these innovations will provide more precise pictures of each cancer based on biological aggressiveness as well as underlying immunogenicity of the TIME. Additionally, clinicians can entertain more tailored therapeutic approaches for the patients based on clear understanding of the landscape of TIME of each tumor. Given challenges to identify respondents to immune checkpoint inhibitors, it might be possible to establish new biomarkers or scoring systems with this approach (10, 11). This bioinformatics approach on immunogenomics will clarify molecular mechanisms of cancer immune responses even further. We believe RNA-sequence and transcriptomic profiling will reveal the enemy King, allowing us to precisely attack and defeat him.

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