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Identifying aggressive forms of endometrioid-type endometrial cancer: new insights into molecular subtyping

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Summary

Clinical heterogeneity represents a great challenge for cancer therapeutics. Molecular classification of patients into different subtypes based on genetic or epigenetic characteristics has the potential to revolutionize the clinical care and mechanistic understanding of a wide spectrum of cancers, including endometrial carcinoma, the most common gynecological cancer affecting women.

Keywords

Molecular subtyping; Endometrial carcinoma; *CTNNB1* mutation; Wnt signaling pathway; Cancer therapeutics

Clinical heterogeneity and complexity represent a great challenge for cancer therapeutics. Cancer classification based primarily on microscopic appearance of the tumor such as stage, grade, or cell lineage has allowed for some successes in individualizing cancer therapy. Microscopic morphology, however, has its limitations when projecting treatment strategies and cancer clinical course. Consequently, oncologists have begun to incorporate genetic classifications to guide clinical decision-making [1]. This approach has revolutionized the clinical care and mechanistic understanding of different cancers. Breast cancer patients are clinically categorized into three intrinsic gene expression subtypes with different therapeutic options [2]. Endocrine therapy is provided to the estrogen receptor (ER) positive group, the *HER2/ERBB2* amplified group receives Herceptin therapy, and triple negative breast cancers are treated with chemotherapy. Mutations in *IDH1* or *IDH2* define a subtype of diffuse lower grade gliomas with favorable prognosis [3]. The Cancer Genome Atlas (TCGA), a collaborative project of the National Cancer Institute and the National Human Genome Research Institute, has recently generated catalogues of multi-dimensional molecular abnormalities in a large population of patient samples in numerous cancer types [4]. In-depth bioinformatic and statistical analysis of the TCGA datasets has revealed new

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molecular subtypes that have potential clinical implications. A G-CIMP phenotype that was characteristic of CpG island methylation and associated with favorable prognosis was recently identified by using the TCGA glioblastoma multiforme datasets [5]. Genetic or epigenetic biomarkers are increasingly used in clinical practice to stratify patients based on difference in survival or response to chemotherapy. High-grade serous ovarian carcinomas with *BRCA2* and to a lesser extent *BRCA1* mutations are deficient in the induction of homologous recombination and therefore have an improved sensitivity to chemotherapy and better survival [6].

Endometrial carcinoma is the fourth most common cancer among women after breast, lung, and colorectal cancer. Approximately 49,560 uterine corpus cases are estimated in the United States in 2013 [7]. There are two broad microscopic subtypes, endometrioid and non-endometrioid. Recognizing these microscopic subtypes is important, as the non-endometrioid carcinomas are typically more clinically aggressive, presenting with advanced stage at the time of diagnosis. Not surprisingly, these two histologies of endometrial carcinoma have distinct molecular aberrations [8]. Molecular clustering of all endometrial carcinoma samples together commonly segregates cases based largely on differences between serous versus endometrioid histologies [8,9]. Endometrioid-type endometrial carcinoma (EEC) accounts for approximately 70–80% of all endometrial cancers, but it is less characterized at the genomic level especially in large patient cohorts. The two isoforms of estrogen receptor (ER α and ER β), encoded by *ESR1* and *ESR2* respectively, have different functions in cancer biology and therapy [10]. In particular, ER α , the predominant isoform in EEC, predicts response to endocrine therapy and is correlated with better survival, while ER β did not demonstrate significant correlations with clinicopathological characteristics [10]. Although many patients with EEC are cured by surgery (hysterectomy) alone without chemotherapy, it is well-known in the oncology community that a subset of these patients will recur. Prediction of which patients who recur is currently not possible.

Identification of Molecular Subtypes of EEC

The clinical heterogeneity of EEC suggests that there are several distinct biological phenotypes that may result from genetic variations that alter oncogenic pathways during tumorigenesis. Recently, we performed an integrated analysis on the multiple-dimensional data types including whole-exome and RNA sequencing, RPPA profiling and clinical data from the TCGA database. We restricted the analyses to EEC (n=271), specifically excluding serous carcinomas, and identified four transcriptome subtypes with distinct clinicopathologic characteristics and mutation spectra [11]. Cluster II (n=61) consisted of younger, obese EEC patients with low-grade, low-stage disease at the time of initial diagnosis, but exhibited a diminished survival compared to Cluster I, which was similarly composed of low-grade, low-stage carcinomas but had higher expression of hormone receptors. *CTNNB1* exon 3 mutations were present in 87% of the carcinomas in Cluster II. High expression of Wnt/ β -catenin signaling downstream targets, such as *Cyclin D1*, were also associated with significantly poorer overall survival. Interestingly, Cluster II has the lowest overall mutation rate of the four clusters, suggesting that this cluster is driven by *CTNNB1* mutation. At about the same time as our TCGA work was being published, Myers et al. demonstrated in a letter to the editor the association of *CTNNB1* mutation with an

increased risk for disease relapse in patients with FIGO Stage 1A, grade 1 endometrioid endometrial carcinoma [12]. This provides independent confirmation that *CTNNB1* mutation is important prognostically for patients with low-grade, low-stage endometrioid carcinomas. In addition, *CTNNB1* alterations are significantly correlated with EEC patients with younger age [11], and have been previously detected in endometrial hyperplasias [13], suggesting that *CTNNB1* alteration is an early event, and plays an important role in endometrial carcinogenesis.

Clinical Insights and Implications

The current clinical dogma for endometrial cancer is that younger patients with endometrioid-type carcinomas are more likely obese with hormone-driven tumors that are low grade and low stage at the time of diagnosis and thus have a better prognosis [14]. Our results clearly show that this group of patients is heterogeneous at the molecular and clinical level. Cluster I, characterized by higher levels of hormone receptors, fits the traditional view of obese endometrial cancer patients and exhibited better clinical outcome. However, Cluster II, also consisting of obese patients, is driven by *CTNNB1* mutations and consequently exhibited a decreased survival compared to Cluster I. Identification of this Cluster II subtype helps to explain, at least in part, the clinical heterogeneity of endometrioid-type endometrial carcinoma.

The *CTNNB1* mutations in Cluster II were primarily confined to a small region in exon 3. This mutational hotspot contains the phosphorylation target for the GSK-3 β kinase, inhibiting its ability to phosphorylate β -catenin (encoded by *CTNNB1* gene) which results in β -catenin accumulation within the cell nucleus and activation of transcriptional programs. Integrated analysis of gene expression profiling showed that genes positively correlated with *CTNNB1* mutation were significantly enriched with components of the Wnt signaling pathway [15]. Using the presence of *CTNNB1* exon 3 mutation, patients could be predicted to have a Cluster II genotype with a sensitivity of 87.0% and a specificity of 88.0%. Of note, the *CTNNB1* mutation hotspot contained almost one-third non-synonymous mutations, resulting in amino acid substitutions of codons 32, 34, and 35 which are not known to be GSK-3 β phosphorylation targets. The effect of these mutations on the β -catenin protein accumulation in the nucleus is not clear yet and warrants functional investigation.

There are several avenues in which this new and exciting data may be clinically translated. Patients with grade 1 or grade 2 EEC may have *CTNNB1* sequencing performed using tumor acquired during the endometrial biopsy to establish diagnosis. Current advance in targeted next-generation sequencing makes *CTNNB1* hotspot mutation sequencing analysis less expensive and clinically practical. For patients with such mutations, more aggressive therapeutic approaches could be considered, such as more extensive surgery to include lymphadenectomy and even post-operative adjuvant radiation treatment and/or chemotherapy. Until recently, specific therapeutic targeting of the Wnt/ β -catenin signaling pathway was not feasible. However, there are now several drugs in early clinical trials. PRI-724 inhibits β -catenin recruitment of its co-activator CBP, thereby blocking transcription of Wnt pathway genes [16]. LGK974 inhibits the O-acyltransferase Porcupine that acylates Wnt proteins for secretion [17]. Cyclin D1 protein interacts with CDK4/6 to

promote cell cycle progression. LEE001 is CDK4/6 inhibitor that could potentially benefit patients with *CTNNB1* mutant endometrial carcinomas [18]. *CTNNB1* genotyping could also provide value in women with endometrial hyperplasia or grade 1 EEC who are being managed conservatively with some type of progesterone preparation, such as the Mirena IUD [19]. It is known that a subset of these patients will not completely respond to such conservative treatment. Based on our previous analyses, it is plausibly speculated that the non-responders may have tumors with *CTNNB1* mutation, as these tumors typically have relatively lower expression of the hormone receptors and are not characterized by high expression of estrogen-induced genes. More effective conservative management of these *CTNNB1* mutant tumors might be achieved by adding another agent to the progesterone regimen, such as a PI3K/AKT/mTOR inhibitor, as mutations in this signaling pathway are common across all subtypes of EEC. Similar to the agents targeting mutant *IDH1* and *IDH2* [20], drugs that can directly inhibit mutant *CTNNB1* can be developed in the future and will certainly benefit the EEC patients with this mutation. In summary, the identification of this second cluster of patients with endometrial cancer helps to refute the long-standing knowledge that young, obese patients universally have endometrial cancers that are estrogen-driven and thus have a good prognosis and may help pave the way for more individualized therapy of endometrial cancer patients.

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