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GENETICS

New classification for endometrial cancer puts genes in *POLE* position

Results that have been published by The Cancer Genome Atlas (TCGA) Research Network in a range of cancers have revealed novel insights into their genetic background and potential targets for therapy. Now, it's the turn of endometrial cancer. Douglas Levine has led the team in assessing the genome, transcriptome and proteome of 373 endometrial carcinomas, and the insights gained could rapidly translate to the clinic.

Endometrial cancer is the fourth most common malignancy in women in the USA. Although patients usually present with early stage disease, in those with aggressive, high-grade tumours that have spread beyond the uterus, disease progression is likely to occur within a year. Increased knowledge of this disease could, therefore, lead to new ways to stratify and treat patients.

Regarding the present study, "endometrial cancer has not had such vast and integrated molecular studies previously performed." Levine explains, "we have known about commonly mutated genes in this disease, but the depth of knowledge reported in the current paper is unprecedented for endometrial cancer."

Indeed, prior to the publication of these data, endometrial cancer was broadly divided into two groups: type I endometrioid cancer (with a favourable prognosis) and type II endometrioid cancer (usually serous type with a poor prognosis). Once diagnosed with type I or II disease, the adjuvant treatment regimens available to a patient are very different; type I tumours are usually treated with radiotherapy, whereas type II tumours are treated with chemotherapy.

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The most significant findings from this in-depth analysis were that "we identified four integrated genomic subgroups that can be used to reclassify endometrial cancers," says Levine. The first subgroup had an increased level of mutations in the *POLE* gene and was associated with improved survival; the second group was the microsatellite instability ultramutated group; the third was the copy-number low group; and the fourth was the copy-number high group. Importantly, as Levine points out: "the copy-number high group contains all the serous tumours that generally have a worse outcome, but also contains about 10% of the endometrioid tumours."

The genetic overlap between some endometrioid tumours and the more-aggressively treated serous cancers indicates that 10% of patients with endometrioid cancers should be receiving additional therapy after surgery. As Levine says: "this classification is completely new and will hopefully lead to improved patient stratification of treatments."

The clinical significance of the four subgroups identified in this study remains to be determined. And so, in collaboration with the Gynecologic Oncology Group, a clinical trial is underway. It is hoped that this information will benefit patients.

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