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Epigenetic silencing of the HAND2 tumor suppressor promotes endometrial cancer

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A study published this week in *PLOS Medicine* suggests that epigenetic modification of the HAND2 gene plays a critical role in the development of endometrial cancer. HAND2 is active in the healthy endometrium (the tissue lining the uterus) where it antagonizes the growth-inducing effects of estrogen. By contrast, in more than 90% of endometrial cancers, the gene has undergone hypermethylation, an epigenetic modification that doesn't change its DNA sequence but renders it inactive.

Martin Widschwendter from the University College London Women's Cancer Department and colleagues, the authors of the work, systematically compared methylation patterns in endometrial cancers and normal endometrium. Using a new bioinformatics tool, they identified HAND2 as a differential methylation hotspot in endometrial cancer. By comparing with other already known factors, HAND2 methylation is by far the most common molecular alteration in endometrial cancer.

The researchers found that HAND2 methylation is already increased in premalignant endometrial lesions (cancer-prone, abnormal-looking tissue) compared to normal endometrium, and that a high level of methylation predicted a poor response to progesterone treatment (which stops the growth of some pre-cancerous endometrial lesions).

Moreover, analysis of HAND2 methylation in endometrial secretions collected from women with postmenopausal bleeding (which can be a symptom of endometrial cancer) accurately identified individuals with

early stage cancer. Finally, mice in which the Hand2 gene was specifically deleted in the endometrium developed precancerous endometrial lesions with age. Widschwendter, who led the study, said: "Our work provides clear evidence that it is not only genetic alterations which trigger and lead to cancer but that epigenetic alteration can also be the initiating step." Endometrial cancer is the most common gynecological cancer, and its incidence is continuing to rise in an older and more obese population. The authors suggest that HAND2 methylation "could be applied to triage women who present with postmenopausal bleeding (currently ~90% of women who present with this symptom and are cancer-free must undergo endometrial biopsy for a definitive diagnosis) and could be further employed as a test to early detect or even predict the risk for endometrial cancer and response to preventative treatment".

More information: Jones A, Teschendorff AE, Li Q, Hayward JD, Kannan A, et al. (2013) Role of DNA Methylation and Epigenetic Silencing of HAND2 in Endometrial Cancer Development. PLoS Med 10(11): e1001551. DOI: 10.1371/journal.pmed.1001551

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