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Genetic landscape of endometriosis- new insights from genome-wide analysis

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One of the most fundamental questions relating to endometriosis research is how endometriosis develops. Endometriosis affects ~10% of reproductive-aged women, causing morbidity such as pelvic pain and infertility. It is defined as the presence of ectopic stromal and epithelial endometrium. Endometriosis is considered as a benign inflammatory lesion, but has cancer-like features such as local invasion. There are three anatomic sub-types of endometriosis: superficial peritoneal endometriosis, ovarian endometriotic cysts, and deep infiltrating endometriosis (DIE). In this study, we focused on elucidating the molecular genetic alterations in DIE. Exome sequencing revealed somatic mutations in 20 (83%) of 24 cases. Five harbored known cancer driver mutations in *ARID1A, PIK3CA, KRAS,* or *PPP2R1A*. Targeted sequencing uncovered *KRAS* mutations in 5/15 additional cases. Taken together, 10 (26%) of 39 deep infiltrating lesions carried driver mutations, all confined to epithelium. Next, we applied digital PCR and analyzed mutations in the known synonymous genes (mutations do not change amino acids) and cancer passenger genes (mutations do not cause cancer) which were neutral in clonal evolution in 14 DIEs. Like cancer driver mutations, all these "neutral" somatic mutations examined were exclusively detected in the epithelial but not in the stromal component in all cases analyzed. Analysis of mutant allele frequency showed ubiquitous involvement of epithelial cells by a given mutation. The above results unequivocally establish clonality involving epithelial cells but not in endometrial stromal cells within a given lesion. Based on the above findings, we propose a possible model in developing DIE- that epithelial progenitor cells from endometrium can survive ectopically, especially when they harbor cancer driver mutations. Once residing in an ectopic site, these epithelial progenitor cells recruit blood-born mesenchymal stem cells to differentiate into endometrial stroma cells on site. Our unexpected findings also suggest a new research direction to study the pathogenesis of endometriosis and may lead to the generation of a biologically informed classification to ultimately improve prognostication and personalize treatment.

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