**Loss of *Cdh1* and *Trp53* in the uterus induces chronic inflammation with modification of the tumor microenvironment**

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Last year, we reported the effects of conditional ablation of *Cdh1* and *Trp53* in the uterus using *Pgr-*driven *Cre*. At 2 months of age, mice with conditional ablation of *Cdh1* and *Trp53* (*Cdh1d/d Trp53d/d*) showed abnormal uterine development (metaplasia) including epithelial invasion into the myometrium, abnormal glandular development, as well as loss of PGR and ESR1. These results indicate that ablation of *Cdh1* and *Trp53* induces invasive phenotypes of endometrial carcinomas without steroid hormone signaling. However, *Cdh1d/d Trp53d/d* mice at 2 months of age did not exhibit any evidence of metastasis to the peritoneal cavity and distant organs. Our subsequent studies examining 6-month old *Cdh1d/d Trp53d/d* mice clearly demonstrate architectural features characteristic of type II endometrial carcinomas, including focal areas of papillary differentiation, protruding cytoplasm into the lumen (hobnailing) and severe nuclear atypia. Further, *Cdh1d/d Trp53d/d* tumors in 12-month old mice were highly aggressive, and metastasized to nearby and distant organs within the peritoneal cavity, such as mesentery and peri-intestinal adipose tissues, demonstrating that tumorigenesis in this model proceeds through the universally recognized morphologic intermediates associated with type II endometrial neoplasia. We also observed abundant cell proliferation and complex angiogenesis in the uteri of *Cdh1d/d Trp53d/d* mice. Our microarray analysis found that most of the genes regulated in the uteri of *Cdh1d/d Trp53d/d* mice were categorized by their involvement in inflammatory responses. The gene transcripts in *Cdh1d/d Trp53d/d* tumors were confirmed by quantitative RT-PCR. This finding clearly highlighted that many genes, especially those related to inflammation, were upregulated in *Cdh1d/d Trp53d/d* tumors, but not in single ablation of *Trp53* or *Cdh1* uteri. We also confirmed that key molecules related to inflammatory signaling, such as p-STAT3, cytokines, chemokines, MMPs and COX2 were abundant in the uteri of *Cdh1d/d Trp53d/d* mice. Thus, these results indicate that the tumor microenvironment under chronic inflammation represents a central regulator of tumor development leading to cell invasion, dissemination and metastasis. Further, CD68 and CD163, markers for tumor associated macrophages, were also detected in the uteri of *Cdh1d/d Trp53d/d* mice, suggesting that an inflammatory tumor microenvironment, with immune cell recruitment, is further augmenting tumor development in *Cdh1d/d Trp53d/d* uteri. In summary, ablation of *Cdh1* and *Trp53* in the mouse uterus initiates chronic inflammation with modification of the tumor microenvironment and promotes aggressive endometrial carcinomas.

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