p53 suppresses type II endometrial carcinomas in mice and governs endometrial tumour aggressiveness in humans

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Type II endometrial carcinomas are a highly aggressive group of tumour subtypes that are frequently associated with inactivation of the TP53 tumour suppressor gene. We show that mice with endometrium-specific deletion of Trp53 initially exhibited histological changes that are identical to known precursor lesions of type II endometrial carcinomas in humans and later developed carcinomas representing all type II subtypes. The mTORC1 signalling pathway was frequently activated in these precursor lesions and tumours, suggesting a genetic cooperation between this pathway and Trp53 deficiency in tumour initiation. Consistent with this idea, analyses of 521 human endometrial carcinomas identified frequent mTORC1 pathway activation in type I as well as type II endometrial carcinoma subtypes. mTORC1 pathway activation and p53 expression or mutation status each independently predicted poor patient survival. We suggest that molecular alterations in p53 and the mTORC1 pathway play different roles in the initiation of the different endometrial cancer subtypes, but that combined p53 inactivation and mTORC1 pathway activation are unifying pathogenic features among histologically diverse subtypes of late stage aggressive endometrial tumours.
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