Correspondence – Histopathology

Primary mucinous ovarian neoplasms rarely exhibit a germ cell histogenesis

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Conflict of interest statement: The authors declare no conflicts of interest

Word count: 541

Recently, genetic analyses of primary mucinous ovarian tumours (MOT) have considerably enhanced our understanding of the biology of such neoplasms, supporting a progressive model of carcinogenesis from benign/borderline tumours to carcinomas (1). Nevertheless, the histogenesis of these neoplasms remains a subject of discussion and several cell types of origin have been proposed; a proportion of these tumours are associated with Brenner (transitional cell) tumours, therefore some are believed to be derived from metaplastic mucinous epithelium

lining cystic transitional cell nests (Walthard rests) (2). Rarely, MOT may arise in the context of ovarian teratoma. In such cases genomic studies have shown the mucinous neoplasms to share identical genetic patterns with the adjacent teratoma, indicating a shared cell of origin (3, 4). Ovarian teratoma are believed to develop from a retained oocyte within the ovary. Extensive loss of heterozygosity (LOH) and extremely low mutational burden are the genetic hallmarks of teratoma, implicating meiotic abnormalities during different stages of germ cell evolution in tumour development (4-6). Although a germ cell origin for the subset of MOT associated with teratomas has been confirmed by multiple studies, such tumours with both mucinous and teratomatous components are rare and the incidence of MOT showing the genetic hallmarks of teratoma, among MOT in which no teratoma is identified, remains unknown.

In an attempt to contribute data to the ongoing discussion on the histogenesis of MOT, we studied the incidence of germ cell derived tumours by investigating genetic characteristics of ovarian teratoma in a large multicenter cohort of primary ovarian mucinous neoplasms. Sequencing data from 265 MOT, including 22 mucinous benign cystadenomas, 36 mucinous borderline ovarian tumours (MBT), 180 primary mucinous ovarian carcinoma (MOC) and 27 extraovarian metastases of MOC were analyzed for widespread LOH, the genetic hallmark of teratomas. These cases are part of the Genomic Analysis of Mucinous Tumours (GAMuT) cohort which represents a large international effort to collaboratively study mucinous ovarian cancers and has previously been described in detail, including pathology and clinical review to exclude non-ovarian primary tumours (1, 7). Patients provided informed consent for the use of their specimens for research and this study was conducted according to the Declaration of Helsinki.

We identified one MOC (1/265; 0.4%) from a 47-year-old patient that showed almost complete copy number neutral LOH (Figure 1), strongly suggesting that this tumour developed from a post meiotic germ cell. Targeted sequencing revealed a pathogenic *KRAS* mutation in this case. The MOC was associated with a component of MBT, completely replacing the left ovary. No adjacent teratoma was reported, however the 16 cm mass showed extensive necrosis. This MOT may have developed as a monodermal teratoma (8), may have outgrown a teratomatous component, or there may have been a teratoma present that underwent necrosis. Furthermore, a second case in the cohort was a MBT associated with an ipsilateral mature teratoma, however genetic analysis revealed a heterozygous genotype in this case. This may either suggest development of

both components from a pre-meiotic primordial germ cell (4, 9), or independent development of the MBT and teratoma in this case.

In conclusion our results indicate that MOT of germ cell origin are exceptionally rare, based on analysis of a large series of unselected cases. While a large majority of MOT are of non-germ cell origin, their histogenesis remains incompletely understood.

Acknowledgement: Detailed information on the GAMuT cohort and its collaborators can be found at "https://gamutstudy.wordpress.com/research-project/study-team/". DC, MJW, CLS, IGC and KLG performed sequencing and bioinformatic analysis of the GAMuT cohort. FKFK and CBG drafted the manuscript which was reviewed and approved of by all authors.

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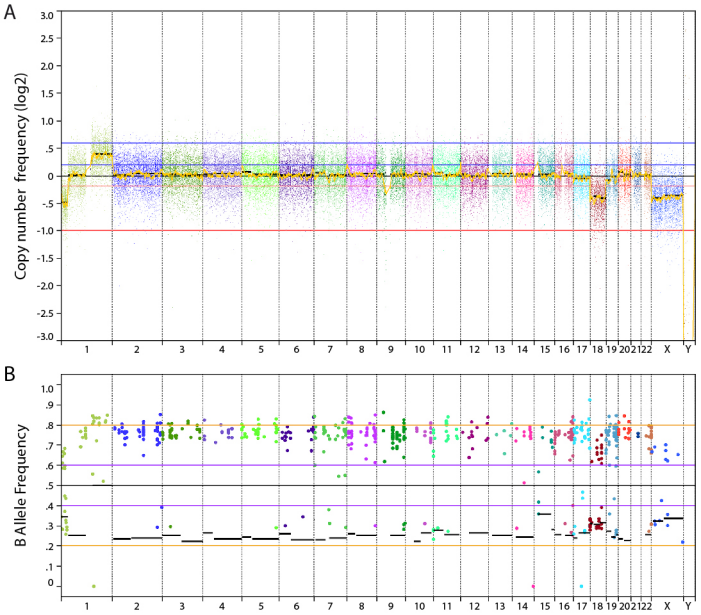
Figure 1: Targeted DNA-sequencing analysis identified one case of mucinous ovarian carcinoma with few changes in copy number (**A**) but widespread loss of heterozygosity in the B allele frequency (**B**), indicating almost complete copy number neutral loss of heterozygosity.



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