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Ovarian low-grade serous carcinoma likely deriving from the fallopian tube

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Background: As a leading cause of cancer deaths among women, ovarian serous carcinoma can be further categorized into high-grade serous carcinomas (HGSC) and low-grade serous carcinomas (LGSC). While compiling data from past decades have suggested that the vast majority of HGSC arise from fallopian tube instead of the ovary itself, the cell of origin LGSC remains controversial. Our recent study based on the morphologic and immunophenotypic features of LGSCs suggests that most LGSCs may also be derived from the fallopian tube and likely derived from tubal secretory cells through a secretory cell expansion process. The current study is designed to explore the genetic basis of the cellular origin and oncogenesis of LGSC.

Design: Gene expression profiles were studied in 44 samples including 11 LGSCs, 7 serous boarderline tumors (SBT), 6 serous cystadenomas (SC), 6 ovarian epithelial inclusions (OEI), 7 Fallopian tubal epithelia (FTE), and 6 ovarian surface epithelia (OSE). Correlation analyses of ovarian serous tumors including its precursor OEIs with FTE and OSE samples were performed by unsupervised hierarchical clustering. Rank-sum analyses and Pearson correlation tests were then applied to determine the likelihood of cellular origin of LGSC and its precursors. Final validation was done on the selected genes and corresponding proteins.

Results: LGSC share gene expression profile significantly with FTE cells, as well as with OEI and serous tumors, yet differently from that of OSE. Furthermore, phylogenetic tree produced by unsupervised hierarchical clustering showed ovarian serous tumors are hierarchically clustered with OEIs and FTE, but separated from OSEs. After ascertaining the reliability of sequencing data, we found that OVGP1, WT-1, and FOM3 highly expressed in samples of the fallopian tube, OEI, and ovarian serous tumors, but not in OSE. In contrast, ARX and FNC1 were mainly expressed in OSE, but not in other studied samples.

Conclusions: This study provides molecular evidence that ovarian LGSC most likely originates from the fallopian tube rather than from ovarian surface epithelia. Similar gene expression profiles among FTE and OEI, and serous tumors further support that the majority of LGSC develops in a step-wise fashion. Such findings may have significant implications for "ovarian" cancer-prevention strategies.

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