MAPPING SEX STEROID HORMONE SIGNALLING IN FALLOPIAN TUBES AS SOURCES OF HIGH-GRADE SEROUS OVARIAN CANCER PRECURSORS AT SINGLE-CELL RESOLUTION

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High-grade serous ovarian cancer (HGSOC) is the most lethal subtype of ovarian cancer, primarily because it is often diagnosed at advanced stages. The early molecular mechanisms driving ovarian carcinogenesis remain poorly understood, which complicates efforts to develop effective prevention and early detection strategies. Most HGSOCs originate from serous tubal intraepithelial carcinomas (STICs) at the distal (fimbrial) end of the fallopian tube (FT), which opens to and is in closest contact with the ovaries. STICs are believed to develop from secretory epithelial FT cells in a gradual, stepwise process over decades. During the evolutionary trajectory of HGSOC precursor lesions, which begins during the reproductive period of life, sex steroid hormone signalling may play an important role, as sex steroids circulate at higher concentrations then compared to older age and fluctuate monthly between high and low levels during the menstrual cycle. In our study, we investigate sex steroid hormone metabolism and signalling in FTs at a single-cell resolution.

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We analysed the gene expression of sex steroid receptors, as well as steroidogenic and steroid-metabolizing enzymes, across different cell populations in normal pre- and postmenopausal FTs using publicly available single-cell RNA sequencing datasets (1, 2).

Our gene expression analyses revealed that the co-expression patterns of sex steroid receptors, specifically oestrogen receptor α (ESR1), progesterone (PGR) and androgen (AR) receptors in secretory epithelial cells differ between pre- and postmenopausal FTs. More specifically, in premenopausal FTs, over 75% of the secretory cell population displayed high positivity only for AR along the entire tube length, whereas in postmenopausal FTs, the high AR positivity of this cell population was accompanied with high ESR1 and PGR expression as well. These differences suggest that sex steroid hormone actions on secretory epithelial FT cells are regulated differently with age, potentially explaining the differing impacts of oral contraceptives and hormone replacement therapy on HGSOC risk. Additionally, secretory and stromal cells in both pre- and postmenopausal FTs expressed enzymes involved in the formation and inactivation of genotoxic catechol oestrogens. Alterations in the formation/inactivation mechanisms of these metabolites could contribute to the dysplastic transformation of secretory cells, ultimately leading to the development of HGSOC precursor lesions.

Secretory epithelial FT cells represent a key cell population where targeted modulation of sex steroid hormone metabolism and signalling could potentially prevent or limit the formation of precursor lesions for HGSOC.

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References

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