Establishing patient-derived organoid cultures as a preclinical model of ovarian cancer

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Background

Ovarian cancer (OC) is the most frequently diagnosed gynecological malignancy in women and has the highest mortality rate (i.e. 51% in 5 years [1]). A lack of screening methods and late disease detection are the main cause of resistance to platinum-based chemotherapy and poor outcomes[2]. While 20-30% of patients develop chemoresistance during primary treatment, this number goes up to 80% for patients who had an initial good response but relapsed over time.

A few targeted therapies like PARP inhibitors, directed a critical proteins of the DNA repair pathway, have been approved for OC treatments, however they associate with severe adverse effects such as hematotoxicity[2]. Moreover, OC displays extensive cellular heterogeneity, which renders monotherapies ineffective.

Thus, a better understanding of the mechanisms driving OC is urgently needed to develop new detection strategies and more effective treatments.

In the last decade, 3D organoids have emerged as a new experimental approach to culture patient biopsies and test response to drugs. OC organoids can be seen as mini-replicas of primary tissues as they recapitulate histological and genomic features of the original tumour, as well as features of tumour heterogeneity[3] *in vitro*. We will establish a collection of OC organoids as a new tool to facilitate personalised treatments and ultimately improve survival of OC patients.

Aims

1) To establish a collection of OC organoids from primary tumours
2) To characterise tumour biopsies and patient-derived OC organoids using histological and genetic techniques
3) To investigate genetic and molecular profiles of patient-derived OC organoids and inform new treatments to overcome therapy-resistance

Methods

1) Collection of OC tissues from patients

Informed consent will be obtained prior to ovarian surgery. OC biopsy will be excised and processed for freezing, to generate FFPE-blocks, and to establish organoid cultures (**Fig. 1A**).

2) Processing and plating of patient-derived OC organoids

OC organoids will be passaged and expanded for banking and further testing.

3) Validation of OC organoids

Following growth and expansion, individual OC organoids will be processed and histologically characterised to define OC subtype (**Fig. 1B**). The presence of OC biomarkers in primary tissues and in derived OC organoids will be comparatively assessed.

4) Characterisation of OC organoids

The profile of genetic and molecular markers of interest will be assessed in OC organoids vs core biopsies, and response to candidate drug treatments will be evaluated (**Fig. 1B**). A dose-response study will allow identification of drug-resistant and drug-sensitive OC organoids. These data will be compared with patient treatment efficacy and clinical outcomes.

Research

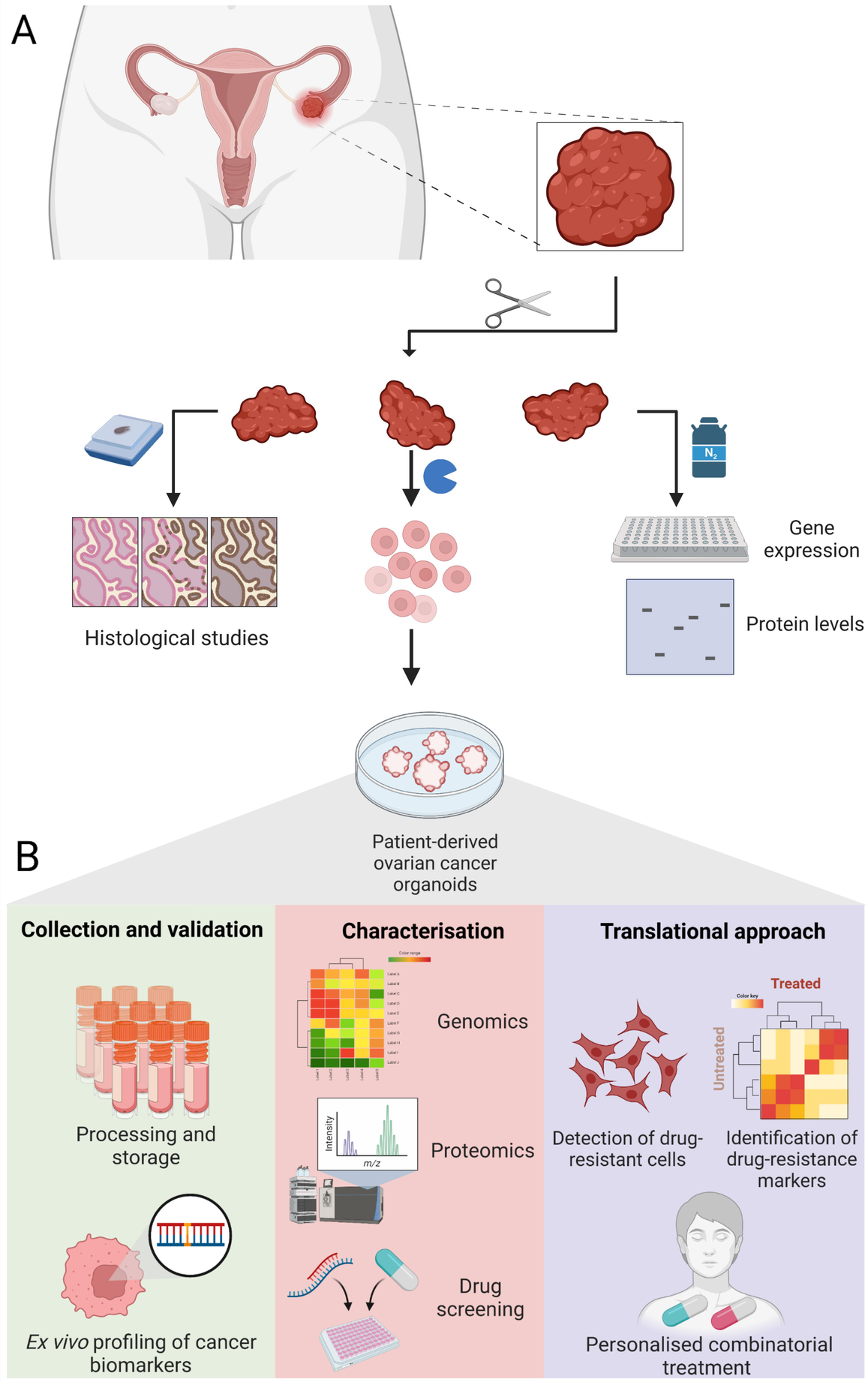

Figure 1. ***Establishing patient-derived OC organoids.*** **(A)** Workflow used for the generation of OC organoid cultures. After collection, the primary tissue is excised for freezing, FFPE-blocks and to establish OC organoids. **(B)** Clinical applications of OC organoids, including collection of OC organoids, characterisation, drug screening and evaluation of treatment response and resistance, to enable precision medicine for OC patients (*Figure created with Biorender).*

Conclusion

Establishing a bio-resource of patient-derived OC organoids will provide a powerful tool to gain new insights into the molecular characteristics of ovarian cancer and screening methods, and will lead to the discovery of novel drug targets for precision medicine.

References

[1]Ovarian cancer statistics in Australia. https://www.canceraustralia.gov.au/.
[2]Lukanović, D.; Kobal, B.; Černe, K. Ovarian Cancer: Treatment and Resistance to Pharmacotherapy. *Reprod. Med.* 2022, *3*, 127-140. doi: 10.3390/reprodmed3020011.
[3]Yang J., Huang S., Cheng S., Jin Y., Zhang N., Wang Y. Application of Ovarian Cancer Organoids in Precision Medicine: Key Challenges and Current Opportunities. *Front. Cell Dev. Biol.* 2021, 9:701429. doi: 10.3389/fcell.2021.701429.