Endometrial and ovarian cancer genomic characterization: a tool toward precision oncology

Heterogeneity remains one of the key points to face concerning cancer management. Cancer shows different characteristics depending on location, cell of origin and, in particular, molecular portrait, being fundamentally a genomic disease suffering from a dysregulation of key oncogenic pathways influencing cell growth and survival. The thorough molecular cancer characterization now available has led to disease definition by organ of origin being questioned. It is no longer considered unusual that cancers of disparate organs have many shared characteristics, while cancers from the same organ may often be quite different. Based on the new patho-molecular characterization, cancers in the same organ – particularly in the case of ovarian cancer (OC) – can be considered "a series of molecularly and etiologically distinct diseases that simply share an anatomical location" [1]. Also, in the case of endometrial carcinomas (EC), broadly classified into type I and type II, the precise pathological and molecular disease definition may influence therapy strategies.

The Cancer Genome Atlas (TCGA) project is aimed at analysing a large panel of human tumours to discover molecular aberrations at DNA, RNA, protein and epigenetic levels. The analyses have been performed in large numbers of tumour samples to improve the ability to detect rare driver events in heterogeneous tumour samples, and to develop an integrated picture of commonalities and/or differences across tumour lineages. OC and EC are among the tumours included in the TCGA project [2, 3].

Almost 500 high-grade serous OC (HGS-OC) cases have been analysed for messenger RNA expression, microRNA expression, promoter methylation, DNA copy number and exome sequencing for 316 genes [2]. Integrated analysis of the data, besides confirming TP53 mutation in more than 96% of the cases, showed significant recurrent somatic mutations, although at low prevalence, in nine further genes, including BRCA1 and BRCA2, resulting in mutations in 22% of cases (a combination of germline and somatic mutations). These data shed new light on the impact of these mutations on patients' survival. Analysis of pathway alterations showed a defective homologous recombination in about half of the analysed tumours, partially explaining the high prevalence of somatic copy number alterations, and involvement of NOTCH and FOXM1 signalling in HGS-OC pathophysiology [2]. The mutation spectrum of HGS-OC is completely distinct from that of other OC histological sub-types, reflecting a combination of aetiological and lineage effects that can influence therapeutic decisions.

The TCGA molecular profiles, made publically available, allowed for further and more thorough analysis of OC genomic alterations. Long not coding RNAs (lncRNAs) are emerging as regulators of cell physiology, having different roles both at cytoplasmic and nuclear levels, and, as in the case of all regulatory molecules, their dysregulation may be involved in

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oncogenesis. By combining genomic copy number data and transcriptome sequencing, a particular lncRNA (OVAL) has been identified as an independent target of gene amplification [4]. Although the putative role of OVAL still needs to be defined, its identification as a specific target of somatic copy-number alteration has underlined the power of TCGA data.

The same integrated genomic, transcriptomic and proteomic characterisation has been done for almost 400 EC cases. Uterine serous tumours are similar to high-grade endometroid tumours, having extensive copy number alterations, few DNA methylation changes and frequent TP53 mutations. Conversely, most endometroid tumours have few copy number alterations or TP53 mutations. For a subset of these tumours (7%), a new hotspot mutation, associated with an extremely good prognosis, has been identified in POLE, a catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair [3].

Analysis of molecular aberrations and their functional roles across tumour types may suggest how to extend therapies effective in one cancer type to others with a similar genomic profile. For instance, the clinical and pathological characteristics of uterine serous carcinoma and HGS-OC are quite similar. Furthermore, HGS-OC shares many molecular similarities with basal-like breast carcinoma, suggesting new opportunities for overlapping treatments.

Deciphering cancer heterogeneity may help in changing the way clinical trials should be designed to achieve a precise oncological management, considering the careful alignment of cancer molecular characteristics, target, drug, patient and trial design.

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