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PROGNOSTIC BIOMARKERS FOR ATYPICAL ENDOMETRIAL HYPERPLASIA: A MINI REVIEW

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Introduction/Background* Atypical hyperplasia (AH) or endometrioid intraepithelial hyperplasia (EIN) refer to a pre-cancerous proliferation of the endometrial glands resulting in an increased ratio of glands to stroma (>3:1). We aimed to identify Immunohistochemistry (IHC) biomarkers to distinguish AH/EIN lesions associated with synchronous endometrioid cancer (EC) or imminent progression to EC.

Methodology We performed a structured review of the published evidence on MEDLINE from inception to March 6, 2021 and selected the 5 most common “themes” (IHC biomarkers) as defined by the number of available studies and/or specimens included. We synthesised the evidence to provide a consensus on their prognostic value (synchronous cancer or imminent progression).

Result(s)* We identified 52 studies from 18 countries. The 5 most discussed biomarkers (“themes”) were: Phosphatase and TENSin homolog (PTEN), stromal expression of p16 protein, nuclear localisation of b-catenin, Paired box gene 2 (PAX2), B-cell Lymphoma 2 expression (bcl-2). PTEN loss in AH was associated with increased risk of Endometrial Cancer (EC). Increased stromal p16 was observed in most EC specimens as well as AH compared to benign; EC had the highest expression. Nuclear β -catenin expression seems to increase from benign to pre-malignant AH but not from pre-malignant to EC. A progressive decrease of PAX2 expression was noted in transition from AH to EC.

Conclusion* Identification of the most common IHC biomarkers whose expression alter during the transition from benign to AH and subsequently EC can flag those cases that immediate definitive management with hysterectomy is needed. This is important when fertility plan is an argument against hysterectomy. Introduction of artificial intelligence algorithms provides the advantage of integrating multiple diagnostic markers in a single prognostic model.

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INFLAMMATORY IMMUNE MICROENVIRONMENT IN CERVICAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS PREDICTS RESPONSE TO TOPICAL IMIQUIMOD IMMUNOTHERAPY

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Introduction/Background* The treatment of cervical high-grade squamous intraepithelial lesion (cHSIL) by topical imiquimod (Aldara®) is investigated as an alternative for surgical large

loop excision of the transformation zone (LLETZ), because of the latter's risk of causing cervical insufficiency and subsequent premature birth in following pregnancies. Imiquimod is effective in ~60% of cHSIL patients, at present we are not able to select women likely to successfully respond. Therefore, studies on predictive biomarkers are needed to enable personalised therapy and to prevent unnecessary potential side effects. Here, we performed an in-depth analysis of the role of the pre-existing immune microenvironment in cHSIL in response to topical imiquimod.

Methodology Histologically confirmed cHSIL of 35 patients biopsied before and 10 weeks after treatment with topical imiquimod were analyzed by two multispectral seven-color immunofluorescence panels to investigate the T cell (CD3, CD8, FOXP3, PD1, TBET, TIM3, DAPI) and Myeloid cell (CD68, CD163, CD11c, CD14, CD33, PDL1, DAPI) composition in relation to treatment response. All 70 samples were scanned with the Vectra multispectral imaging system. Cells were automatically identified using a deep learning multispectral image analysis approach (inForm software).

Result(s)* Our data show that the immune microenvironment of complete responders (CR) prior to imiquimod therapy is characterized by a coordinated infiltration with T helper cells (activated PD1+/type 1 Tbet+) and pro-inflammatory M1 macrophages (CD68+CD163-) and dendritic cells (CD11c+). The lesions of non-responders (NR) lacked such a pro-inflammatory response and displayed an impaired influx of these pro-inflammatory lymphoid and myeloid cells. In contrast, the NR showed an increased infiltration by immunosuppressive regulatory T cells (CD3+FOXP3+). After 10 weeks of topical imiquimod application, the influx of pro-inflammatory CD4+ and CD8+ T cells was further increased in the CR but not in the NR patients, and the infiltration by macrophages was decreased.

Conclusion* Response of cHSIL to topical imiquimod is associated with the presence of a pre-existing pro-inflammatory process, resulting in the coordinated influx of several types of immune cells, which is then further amplified. Our findings indicate major potential of the immune microenvironment as predictive biomarker for the selection of cHSIL patients responding to topical imiquimod immunotherapy.

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PATIENT-DERIVED ORGANIDS REFLECT INTRA-TUMOURAL HETEROGENEITY IN HIGH GRADE SEROUS OVARIAN CANCER

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Introduction/Background* High Grade Serous Ovarian Cancer (HGSOC) frequently presents at an advanced stage with widespread disseminated disease. The majority of patients will ultimately relapse and develop platinum resistance. HGSOC is characterised by a high degree of genomic instability and heterogeneity which is not accounted for in current 2D cell line and murine models. 3D ex-vivo models such as patient-derived organoids (PDOs) are better able to recreate tumour

architecture and microenvironment. In this study, we aim to generate multisite PDOs to demonstrate the spatial heterogeneity of cancer stem cells (CSCs) and responses to chemotherapy treatments in disseminated HGSOc.

Methodology Tumour cells were extracted from disseminated multisite tumours from chemo-naïve patients undergoing maximal effort cytoreductive surgery at Hammersmith Hospital, UK. PDOs were established by embedding tumour cells in basement membrane extract and in specialised organoid or R-Spondin-enriched media. PDOs were propagated and treated with standard-of-care chemotherapy drugs (cis- and carboplatin, PARPi) to assess drug responses. PDOs were histologically processed for characterisation of tumour markers, and CSCs across multiple tumour sites and passages.

Result(s)* PDOs were established from multisite deposits (n=8 patients, mean = 7 tumours per patient, range = 4 – 10) and confirmed to be of HGSOc tumour origin. Response to R-Spondin-enriched media varied across sites and across patients, but was maintained over multiple passages. PDOs were assessed for expression of known CSC biomarkers (ALDH1, CD117, CD133, CD44). IC50 assays established for standard-of-care chemotherapy drugs demonstrated heterogeneous responses to treatment.

Conclusion* PDOs demonstrated the heterogeneity of the CSC population, growth conditions, and drug responses, reflecting the complexity of HGSOc. Our data suggests that treatment regimens chosen based on drug response from a single tumour site may not be effective against other disseminated tumours. PDOs which include multiple metastatic sites may lead to the development of targeted and personalized treatment strategies which reflect the spatial heterogeneity of HGSOc.

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MOLECULAR LANDSCAPE IN HIGH-GRADE SEROUS OVARIAN CANCER: THE CORRELATION BETWEEN BRCA MUTATIONAL STATUS AND STROMAL P16 EXPRESSION

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Introduction/Background* The effect of BRCA mutational status on biological feature and survival outcome in advanced-stage (IIB-IV stage) High-grade serous ovarian cancer (HGSOc) seems to confer a better prognosis. The aim of our preliminary work is to investigate the stromal p16 expression for HGSOc in advanced-stage (IIB-IV stage), using immunohistochemistry, and differences in the expression status depending on the mutational status of BRCA. Alterations in p16 protein expression have been reported to be associated with tumor development and progression. p16 expression status in the peritumoral stroma has been rarely investigated.

Methodology This is a retrospective study included 33 patients diagnosed with FIGO stage IIB-IV HGSOc who underwent

primary debulking surgery (PDS) at the Departments of Gynecology and Obstetrics of the University of Pisa between January 2019 and April 2020. The stromal p16 expression in HGSOc was investigated by using immunohistochemistry, and the differences in p16 immunoreactivity linked with the BRCA mutational status were analyzed.

Result(s)* BRCA1/2 mutations were observed in 15 women (45%). Wild-type -BRCA advanced HGSOcs exhibited diffuse, moderate-to-strong p16 immunoreactivity in 46.66% of cases, instead mutated-BRCA advanced HGSOcs showed elevated stromal p16 expression in 33.33% of cases.

Conclusion* This study introduces a new and interesting result: the correlation between stromal expression of p16 and BRCA mutational status. The majority of malignant lesions exhibited diffuse and moderate-to-strong p16 immunoreactivity, suggesting that stromal p16 expression can be used as an adjunctive predictive and prognostic biomarker for HGSOc. Further studies are necessary to confirm our preliminary results and to explain the different outcome of wt- and m-BRCA HGSOc.

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THE ROLE OF DAPK1 IN THE CELL CYCLE REGULATION OF CERVICAL CANCER CELLS AND IN RESPONSE TO TOPOTECAN

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Introduction/Background* Cervical cancer is the fourth most common cancers among women worldwide. Primary therapy of cervical cancer depends on the disease extent and is based on radical hysterectomy or chemoradiation. However, therapeutic approaches in metastatic and recurrent disease of cervical cancer are limited. Particular effort in drug development focuses on essential serine/threonine kinases like the death-associated protein kinase 1 (DAPK1) and Polo-like kinase 1 (PLK1) as potential therapeutic targets in cervical cancer.

Methodology and Result(s)* Our study examined the role of DAPK1 during the cell cycle of cervical cancer cells. We found that DAPK1 is autophosphorylated in mitosis, exhibiting only low activity towards exogenous substrates. Furthermore, DAPK1 localizes together with PLK1 at centrosomes, which can phosphorylate DAPK1. Finally, we could show that Topotecan, which is used in different clinical trials to treat cervical cancer, induces cell death, which partially depends on DAPK1. **Conclusion*** Topotecan is an effective drug for the treatment of cervical cancer. We explored the role of DAPK1 in Topotecan-induced cervical cancer cell death and revealed that the RNAi-based silencing of DAPK1 downregulates the apoptotic activity suggesting that DAPK1 could be a biomarker for the response to Topotecan in clinical trials.