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 endometroid 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).

Results* We identified 52 studies from 18 countries. The 5 most discussed biomarkers 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 b-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 immediate definitive management with hysterectomy. 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 AH in response to topical imiquimod.

Methodology Histologically confirmed AH 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, CD1, 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).

Results* 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 AH 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 AH patients responding to topical imiquimod immunotherapy.

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, CD1, 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).

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

Introduction/Background The effect of BRCA mutational status on biological feature and survival outcome in advanced-stage (IIIB-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 (IIIB-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 IIIB-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.

Molecular Landscape in High-Grade Serous Ovarian Cancer: The Role of DAPK1 in the Cell Cycle Regulation of Cervical Cancer Cells and in Response to Topotecan

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.