Mechanisms of dissemination and molecular signatures for advanced diagnosis, outcome prediction, and tailored management of ovarian cancer

Key molecules in ovarian cancer dissemination

Peritoneal dissemination is a particular form of ovarian cancer metastasis which is the cause why the majority of patients are diagnosed at advanced FIGO stage accompanied with ascitic fluid and/or solid implants. Identification of the molecular players involved in ovarian cancer (OC) dissemination can offer an approach to develop treatment strategies to improve clinical prognosis. We have identified several cell surface molecules, which may promote the spreading of ovarian cancer. Here, we describe integrinα2 (ITGA2) as a key factor for cancer cell adhesion to extracellular matrix protein collagen that promotes metastasis to the omentum and promotes the dissemination of selected ovarian cancer cell lines and ex vivo using patient-derived tumor cells. Moreover, we also demonstrate that ITGA2 promotes directed cell migration and mesothelial clearance in coculture systems. Mechanistically, the oncogenic properties rely on ITGA2-dependent focal adhesion kinase and activation of mitogen-activated protein kinase pathways (Huang et al., 2020). In a collaboration with Leonor David (University of Porto, Portugal) we show that mesothelin (MSLN), which is overexpressed in primary and matched peritoneal metastasis of high-grade serous carcinomas, promoted invasion of tumor cells through the mesothelial cell layer in vitro. Intraperitoneal xenografts established with MSLN-high OC cell lines showed enhanced tumor burden and spread within the peritoneal cavity. MSLN is hence suggested as key player in OC progression by triggering peritoneal dissemination (Coelho et al., 2020).

Epithelial-to-mesenchymal transition (EMT) and its reverse MET are suggested to be key features of OC metastasis and metastatic cellular and molecular processes essential for local tumor growth, dissemination, and establishment of metastases at distant sites. We found that loss glycolipid glycosphingolipids (GLSs) through genomic deletion of the key enzyme AGAL7 induced EMT in OC cells, associated with loss of E-cadherin expression (through epigenetic silencing of CDH1) and cell-cell adhesion and increased chemoresistance (Jacob et al., 2018). Our current focus is to understand the role of GSL in MET, identify associated signaling pathways and study the expression of GSLs in patient-derived cells. In collaboration with Arun Everett-Dass and Mark von Itzenheim (Institute for Glycomics, Griffith Uni- versity, Australia), we have established MALDI imaging to study spatial distribution of GSLs in matched and longitudinal tissue samples.

New molecular signatures towards early detection, outcome prediction, and tailored management of ovarian cancer

The identification of markers (signatures) for early and accurate diagnosis and reliable outcome prediction are the key to optimal management of ovarian cancer. In the era of precision medicine, where we transition from organ-based diagnosis towards individual genetically-linked diseases, the tailoring of treatment in cancer becomes increasingly important. This is particularly true for high-grade advanced stage serous adenocarcinomas comprising malignant tumors of the ovary (OC), fallopian tube (TC) and peritoneum (PC). These diseases currently are managed similarly, but our study using transcriptomic and next-generation sequencing data and validation by immunohistochemistry in various patient cohorts indicate that OC and PC are epidemiologically and molecularly distinctly disease entities: PC relies on shared pathways of cell-cell adhesion and increased chemoresistance i.e. proteins are differently and uniquely glycosylated in OC versus PC (Anugraham et al., 2017).

Additional studies from our own group evaluated candidate ovarian cancer detection and outcome markers for HSOGC. Among them the expression of maternal embryonic leucine zipper kinase (MELK) correlated with poor survival (Köhler et al., 2017), whereas LATS expression was not associated with outcome in ovarian cancer patients (Montavon et al., 2019).

Selected Publications


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Personalized Medicine - Metastasis - Therapeutic Strategies

Epithelial-to-mesenchymal transition - Aberrant Glycosylation

Connection to Clinical Practice

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Precision medicine in ovarian cancer management

The tailoring of treatment in cancer is a pivotal for improved treatment regimens. In this respect, one study shows a superior outcome of patients with Malignant mixed Mullerian tumors originating from the endometrium (MMMT-E) treated with plati- num/anthracycline or ifosfamide regimen as compared to those treated with platinum/taxanes regimens, suggesting that the previous shift from anthracycline or ifosfamide-based towards taxane-based chemotherapy for MMMT-E (possibly also for MMMT at the ovary) would be worth reviewing (Heinzelmann-Schwarz et al, 2020). In addition, the potential of immunotherapy for patients with advanced cervical carcinomas is highlighted by the per- sistent complete response after third-line treatment for relapsed chemotherapy-resistant cervical cancer (Baezt et al, 2019). In regards to ovarian cancer, our data suggest Letrozole maintenance treatment improving recurrence-free interval (Heinzelmann-Schwarz et al, 2019). These data are the basis for our initiated MATAO-trial, a phase III multi-center international clinical trial to evaluate the effi- cacy of Letrozole maintenance therapy after stand- ard surgical and chemotherapy treatment in pa- tients with newly diagnosed ER-positive ovarian OC (Pi: Prof. Heinzelmann-Schwarz). We are also part of the Tumor Profiler (TuPro) Con- sortium, an integrated, multi-omic, functional tumor profiling platform for clinical decision support, and currently evaluate the use of various state-of-the-art platforms (www.medrxiv.org/content/10.1101/2020.02.13.20017921v1).

Fig.1: Schematic representation of ITGA2-collagen dependent signaling axis in ovarian cancer metastasis

Cancer cells from primary ovarian tumor are passively (via adhesion) disseminated into the peritoneal cavity and establish a metastatic tumor in the omentum (omentum metastasis). Integrinα2 (ITGA2) promotes ovarian cancer cell adhesion to collagen-rich omentum, promotes directed cell migration, anoikis resistance, mesothelial clearance, and peritoneal metastasis through the activation of MAPK and FAK signaling axis.

Fig.2: Serious peritoneal cancer is more aggressive than high grade advanced stage ovarian cancer. Both cancers display distinct molecular signatures. From: Jacob et al., Mol. Oncol. 2020. doi: 10.1002/1878–0261.12811.