Ovarian Cancer Research

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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 a poor patient's outcome. 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 markers that 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 as demonstrated by *in vitro* assays in gene-edited 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 co-culture systems. Mechanistically, the oncogenic properties rely on ITGA2-dependent phosphorylation of focal adhesion kinase and activation mitogen-activated protein kinase pathways (*Huang et al., 2020;* Fig. 1). 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 comprise cellular and molecular processes essential for local tumor growth, dissemination, and establishment of metastases at distant sites. We found that loss globoside glycosphingolipids (GSL) through genomic deletion of the key enzyme *A4GALT* 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 Everest-Dass and Mark von Itzstein (Institute for Glycomics, Griffith University, 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 distinct disease entities: PC relapsed earlier, had a distinctively different gene signature, and showed a different sensitivity to standard chemotherapy drugs compared to OC (*Jacob et al., 2020)*. A preceding study characterized the N- and O-glycome of these two disease entities using tissue glycomics and revealed also distinct glycomic signatures 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 HGSOC. Among them the expression of maternal embryonic leucine-zipper kinase (MELK) correlated with poor survival *(Kohler et al., 2017)*, whereas LATS expression was not associated with outcome in ovarian cancer patients *(Montavon et al., 2019)*.

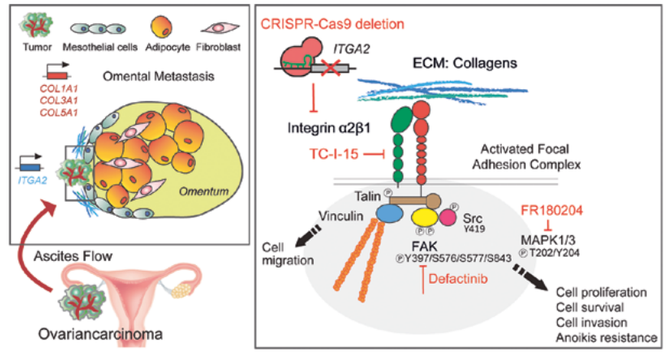

Fig 1: Schematic representation of ITGA2-collagen dependent signaling axis in ovarian cancer metastasis

Left: Cancer cells shed of from primary ovarian tumor are passively (via ascites) disseminate into the peritoneal cavity and establish a metastatic tumor in the omentum (omental metastasis). Integrinα2 (ITGA2) triggers 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.

Right: This process can be inhibited at several levels by deletion of ITGA2 function (disrupts interaction with collagen), by integrinα2β1 inhibitor TC-I-15 (dimerization failure with Integrinβ1), and by inhibition of focal adhesion kinase FAK and mitogen-activated protein kinase MAPK (blocks signaling multiple cellular processes). From: *Huang et al., 2020. eLife.9:e59442. doi: 10.7554/eLife.59442.*

Selected Publications

Huang YL, Liang CY, Ritz D, Coelho R, Septiadi D, Estermann M, Cumin C, Rimmer N, Schötzau A, Núñez López M, Fedier A, Konantz M, Vlajnic T, Calabrese D, Lengerke C, David L, Rothen-Rutishauser B, Jacob F, Heinzelmann-Schwarz V (2020). Collagen-rich omentum is a premetastatic niche for integrin α2-mediated peritoneal metastasis. eLife.9:e59442. doi: 10.7554/eLife.59442.

Jacob F, Marchetti RL, Kind AB, Russell K, Schoetzau A, Heinzelmann-Schwarz VA (2020). High-grade serous peritoneal cancer follows a high stromal response signature and shows worse outcome than ovarian cancer. Mol. Oncol. doi: 10.1002/1878–0261.12811.

Coelho R, Ricardo S, Amaral AL, Huang YL, Nunes M, Neves JP, Mendes N, López MN, Bartosch C, Ferreira V, Portugal R, Lopes JM, Almeida R, Heinzelmann-Schwarz V, Jacob F, David L (2020). Regulation of invasion and peritoneal dissemination of ovarian cancer by mesothelin manipulation. Oncogenesis. 9:61.

Jacob F, Alam S, Konantz M, Liang CY, Kohler RS, Everest-Dass AV, Huang YL, Rimmer N, Fedier A, Schötzau A, Lopez MN, Packer NH, Lengerke C, Heinzelmann-Schwarz V (2018). Transition of Mesenchymal and Epithelial Cancer Cells Depends on α1–4 Galactosyltransferase-Mediated Glycosphingolipids. Cancer Res. 78: 2952-2965.

Heinzelmann-Schwarz V, Knipprath Mészaros A, Stadlmann S, Jacob F, Schoetzau A, Russell K, Friedlander M, Singer G, Vetter M (2018). Letrozole may be a valuable maintenance treatment in high-grade serous ovarian cancer patients. Gynecol Oncol. 148:79–85.

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 platinum/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 of the ovary) may be worth reviewing *(Heinzelmann-Schwarz et al, 2020).* In addition, the potential of immunotherapy for patients with advanced cervical cancer is highlighted by the persistent complete response after third-line treatment for relapsed chemotherapy-resistant cervical cancer *(Baettig et al, 2019).* In regards to ovarian cancer, our data suggest Letrozole maintenance treatment improving recurrence-free interval *(Heinzelmann-Schwarz et al, 2018).* These data are the basis for our initiated MATAO-trial, a phase III multicenter international clinical trial to evaluate the efficacy of Letrozole maintenance therapy after standard surgical and chemotherapy treatment in patients with newly diagnosed ER- positive epithelial OC *(PI: Prof. Heinzelmann-Schwarz).*

We are also part of the Tumor Profiler (TuPro) Consortium, 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).

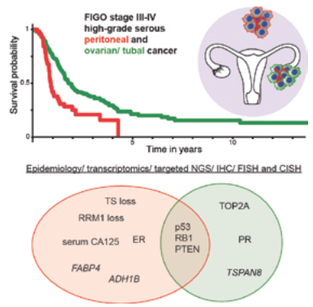

Fig 2: Serous peritoneal cancer is more aggressive than high grade advanced stage serous ovarian cancer. Both cancers display distinct molecular signatures. From: *Jacob et al., Mol. Oncol. 2020.doi: 10.1002/1878–0261.12811.*