Detection and Outcome Markers - Metastasis - EMT - Aberrant Glycosylation

Drugs and Treatment - Tissue Targets

Identification of novel molecular signatures to improve epithelial ovarian cancer outcome

Gynecological cancers in general and ovarian cancer (OC) in particular are the main focus of our research. OC is the fifth most common cause of death from all cancers in women and the leading cause of death from gynecological malignancies, with a poor prognosis (5-year survival <20%). Major issues with OC are its heterogeneity, its unclear genetic origin, its diagnosis at advanced stages due to the lack of accurate biomarker, its ability to rapidly metastasize into other organs, and its insufficient treatment due to disease recurrence (therapy resistance) and missing personalized therapy regimens. Our particular focus is to: (i) identify molecular/genetic signatures that unequivocally discriminate OC patients by their clinicopathological parameters (e.g. histotype, grade, stages) and identify molecular targets for the better prediction of disease outcome and for the design of targeted therapies, (ii) elucidate the molecular basis and biological functions of aberrantly glycosylated proteins and lipids in cancer initiation, progression, and dissemination, (iii) evaluate in clinical studies novel means to improve diagnosis and treatment of gynecological cancers.

Identification of discriminating signatures in the era of omics (Prof. Viola Heinzelmann-Schwarz)

Identification of novel “discriminating” diagnostic and prognostic markers and therapeutic targets is an urgent need in the fight against cancer. Employing various glycan-based immunomass assays we identified sets of specific markers (glycans) that enable us to discriminate healthy controls from ovarian cancer patients with specificity and sensitivity comparable to the current biomarker CA125 (Jacob et al., 2012; 2014; Pochechueva et al., 2011, 2016). We also found particular glycan-based signatures (glycans and glycos-eyes) which distinguish serous ovarian from peritoneal cancers: this, together with transcriptomic and epidemiologic data, provides further evidence that these two cancers are clearly different diseases and hence should no longer be clinically treated as one (manuscript in preparation).

We also identified two protein kinases with significance in ovarian cancer: ROR2, a Wnt-signaling-associated receptor tyrosine kinase, is overexpressed in ovarian cancer patients (tissue microarray) and is implicated in proliferation, migration, and invasion (Henry et al., 2015). MEK1 (maternal embryonic leucine-zipper kinase) was identified as an interesting candidate in ovarian cancer (Heinzelmann-Schwarz et al., 2004) already in 2004 when still known as KIAA0175. We now show in broad transcriptomic/bioinformatical data analyses that MEK1 also evades in ovarian cancer patients, increases with ascending aggressiveness, and correlates with poor disease outcome, and that its inhibitor OTSSP167 is a highly active agent (including drug-resistant) ovarian cancer cells (manuscript in revision).

Regulation and function of specific glycan motifs in ovarian cancer (Glyco-Oncology: Dr. Francis Jacob)

It is acknowledged that glycosylation is crucial to the proper function(s) of glycoproteins and glycophospholipids but the molecular and biological details are poorly understood. Owing the expertise of Francis Jacob as Glycoscientist (the “Glyco-Oncology” branch within Ovarian Cancer Research was launched in 2015, in collaboration with Nicki Packard (Sydney), membrane protein glycan features (“bi- secting GlnNac-type N-glycans) unique to ovarian cancer cells were identified and experimental evidence is provided that expression of MGAT3 (enzyme for bi- secting GlnNac synthesis) is epigenetically regulated by DNA-methylation and correlates with presence of bisecting GlnNac on glycoproteins (Anugraham et al., 2014, Kohler et al., 2016). Likewise, evaluation of 18 TCGA cancer types (618 sam-}

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Selected Publications


Towards improved detection, diagnosis, prediction, and management of gynecological malignancies

The risk of malignancy index (RMI), which allows appropriate preoperative triaging of patients with malignant ovarian tumors and accurate planning of the required surgical procedure, in some cases remains inconclusive. With our “improved” RMI, which includes a mathematical two-step model incor- porating expert pattern recognition, we were able to particularly identify previously undetected ovarian cancer patients (Manegold-Brauer et al., 2014, 2016). One study showed that women with a positive family history generally use mammog- raphy screening more often and perceive changes in the breast earlier than women without such his- tory (Schwab et al, 2014) and another confirms the causal relationship between persistent infection with high-risk HPV genotypes and vulvar and cer- vical cancer (Heinzelmann-Schwarz et al., 2014). Preliminary results from Mito/Mango 16b and NO- VATION clinical trials initiated in 2014 are pending.