PO-287 A NOVEL L1/STAT3 CROSSTALK DRIVES OVARIAN CANCER STEM CELL FUNCTION

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10.1136/esmoopen-2018-EACR25.318

Introduction Ovarian cancer (OC) is the most lethal gynaecological malignancy due to the lack of peculiar symptoms during its onset. Moreover, OC often relapses as a chemoresistant disease within 1–2 years after surgical debulking.

These pathological hallmarks raised the hypothesis that OC is a cancer-stem cell (CSC)-driven disease. Indeed, a 'stem-like' chemoresistant subset in OC is able to form spheroids in suspension cultures and is more tumorigenic respect to the bulk population. This pointed to ovarian CSC (OCSC) as an intriguing target for OC-eradicating therapies.

The cell adhesion molecule L1 (hereafter referred to as L1) has been implicated in OC progression. Furthermore, L1 function has been causally linked to stemness in both embryonic and stem-like cells from different tumours. Finally, a strong correlation exists between L1 expression and shorter 5 year overall and progression-free survival in Stage I/II OC, a subgroup of patients that normally has a relatively good prognosis. This confirms the potential clinical value of L1 in OC. Based on these observations, we aimed to investigate the functional role of L1 in the physiopathology of OCSC.

Material and methods OVCAR3 and Ov90, two OC cell lines with high and low L1 levels, respectively, were employed for loss- and gain-of-function studies. Sphere-forming efficiency (SFE) and tumorigenesis in NSG mice were employed as *in vitro* and *in vivo* assays for cancer stemness, respectively. BBI608 was used as STAT3 activity inhibitor.

Results and discussions L1 was both required and sufficient for self-renewal in OC *in vitro*. Moreover, L1 silencing prevented tumour formation while its forced expression in OCSC-enriched sphere cultures promoted tumour initiation *in vivo*. L1 *per se* was sufficient for OC sphere formation even under very stringent conditions. Mechanistically, L1 dramatically increased the expression and the activation of STAT3 in OCSC. Moreover, STAT3 activity was required for L1-induced OCSC function and, interestingly, L1-induced activation of STAT3 occurred in a JAK-independent manner. Thus, a novel L1/STAT3 axis appears to sustain OCSC pathophysiology.

Conclusion L1 can be considered as a new player and potential target in the context of OCSC, and the L1/STAT3 cross-talk emerges as a novel driver in OC initiation and progression. Therefore, this work might pave the way to novel therapeutic strategies for the eradication of such a devastating disease.

PO-288 REPLICATION STRESS RESPONSE AS A TARGET FOR ERADICATING COLORECTAL CANCER STEM CELLS

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10.1136/esmoopen-2018-EACR25.319

Introduction Cancer stem cells (CSCs) are subsets of multipotent SCs responsible for tumour development, propagation and evolution, whose targeting is required for tumour eradication. There is (pre)clinical evidence on a role of CSCs in therapeutic resistance and intra-tumour heterogeneity, which limits the efficacy of antineoplastic regimens. In this context, CSCs reportedly share with embryonic/adult SCs a very robust DNA damage response, which favours the survival and resistance to genotoxins, and can be exploited for therapeutic purposes.

Material and methods We generated a panel of ~30 CRC patient-derived tumorspheres enriched for CSCs (CRC-SCs) and characterised them at the genetic level. To discover potential monotherapeutic anti-CSC agents, we performed high-throughput screenings on multiple CRC-SCs with a library of clinically-relevant drugs. Flow cytometry, fluorescence microscopy and epistatic analyses were conducted to uncover the mechanism of action of identified compound(s), while genetic, cytogenetic and phosphoproteomic studies were carried out to identify predictive biomarkers. DNA replication stress (RS) levels were evaluated by analysing phosphorylated ATM/RPA foci and by performing COMET and DNA fibre assays, and were modulated by single administration of genome destabilising agents or by prolonged exposure to increased doses of compounds targeting the replication stress response (RSR).

Results and discussions We demonstrated that the CHK1 inhibitor LY2606368 is a potent anti-CSC agent able to kill more than one third of CRC-SCs, both *in vitro* and *in vivo*. Moreover, we provided evidence of high but heterogeneous RS levels in CRC-SCs, showing that, in CRC-SCs, RS is mainly boosted endogenously by p53 deficiency, supernumerary chromosomes and DNA replication abnormalities, which results in high dependency on CHK1-mediated RSR. Accordingly, formerly LY2606368-resistant CRC-SCs were sensitised by boosting DNA replication errors or inducing whole-genome doubling, while formerly LY2606368-sensitive CRC-SCs made resistant by the continuous *in vitro* or *in vivo* administration of LY2606368 displayed diminished RS levels due to RSR rewiring, and became independent on CHK1.

Conclusion Our results demonstrate that RSR is efficient and rewirable in CSCs thereby constituting a prominent therapeutic target. In particular, we designed dedicated RS-modulating or RSR-targeting strategies for long-term CSC depletion in CRC.

PO-289 DUAL INHIBITION OF WNT/β-CATENIN SIGNALLING AND HISTONE DEACETYLATION AS A NEW STRATEGY TO ELIMINATE BREAST CANCER STEM CELLS BY AUGMENTATION OF APOPTOSIS

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10.1136/esmoopen-2018-EACR25.320

Introduction Epigenetic changes play a critical role in the regulation of cancer stem cell (CSC) properties and the development of drug resistance. Modulation of histone acetylation program is closely related to differentiation and apoptosis process. CSCs, a subset of tumour cells, are responsible for disease relapse because of an acquired resistance to apoptosis and the Wnt signalling which is associated with cell survival/self-renewal and differentiation, is re-activated in these cells. Therefore, in the present study, we focused on a possible cytotoxic/apoptotic effect of the