AB054. SOH21AS148. Novel insights into immune-independent functions of immune checkpoint inhibitors in oesophageal adenocarcinoma—potential implications for overcoming chemoresistance to first-line chemotherapy regimens

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Background: Immune checkpoint inhibitors (ICIs) reinvigorate anti-tumour immunity in oesophageal adenocarcinoma (OAC). However, emerging studies have identified novel immune-independent functions for immune checkpoints (ICs) in other solid tumour-types, whereby IC signalling in gastric cancer cells confers chemoresistance. This study explores immune-independent functions of ICs in OAC and if therapeutic blockade may enhance treatment efficacy.

Methods: OAC cells were screened *in vitro* and *ex vivo* for a range of ICs (PD-1, TIGIT, TIM-3, LAG-3, A2aR, PD-L1, PD-L2, CD160) by flow cytometry. The phenotype of OAC cells expressing ICs was also assessed for features of stemness (ALDH, CD54), senescence (β-galactosidase) and invasiveness (vimentin) in the absence and presence of chemotherapy by flow cytometry. Importantly, the effect of ICIs on viability (CCK-8 assay and western blot to assess Bcl-xL), proliferation (BrdU assay), chemo-sensitivity (annexin-V propidium iodide assay), metabolism (seahorse), invasiveness and stemness characteristics (flow cytometry) was assessed in OAC cells.

Results: A subpopulation of stem-like, senescent and vimentin+ cells were enriched for ICs, which was enhanced by FLOT and CROSS. Blockade of PD-1, TIGIT, A2aR, TIM-3 and PD-L1 decreased proliferation, induced apoptosis and enhanced toxicity of FLOT in OAC cells. Blockade of TIGIT decreased pro-survival Bcl-xL factor, induced cell death and promoted a more glycolytic phenotype in OAC cells.

Conclusions: Several novel ICs have been identified as potential targets to enhance chemotherapy efficacy in OAC. Upregulation of ICs on OAC cells following chemotherapy may represent potential mechanisms of chemo-immune resistance for stem-like, senescent and vimentin+ aggressive cancer cell clones. Combination ICIs may be required to enhance efficacy of chemotherapy in OAC patients and warrants further investigation.

Keywords: Immune checkpoints (ICs); chemotherapy; oesophageal cancer; senescence; stem-like cancer cells

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Footnote

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