TARGETING FPR2 AS A NOVEL APPROACH FOR IMMUNOTHERAPY IN PANCREATIC CANCER FEMALE PATIENTS - STUDIES OF SEXUAL IMMUNE DIMORPHISM IN THE TUMOR MICROENVIRONMENT

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Background Immunotherapy for pancreatic cancer (PC) is inefficient due to a highly immune-suppressive tumor microenvironment (TME) orchestrated by myeloid suppressor cells, which limit the infiltration and function of cytotoxic immune cells. We have evidence that accumulation of a subpopulation of myeloid cells in human pancreatic lesions is associated with immune-exclusive tumor phenotype and effector T cell exhaustion by mechanisms involving the G-coupled protein receptor formyl peptide receptor 2 (FPR2), exclusively in women. We hypothesize that female FPR2+ myeloid cells in tumors induce immune exhaustion and contribute to immune-cold tumor phenotype.

Methods To test our hypothesis, we first investigated the FPR2 RNA and protein expression in PC transcriptomic data and in murine and human PC tissues. Further, in vitro cytokine differentiated, alternatively tumor conditioned myeloid cells (TCM) were co-cultured with T cells to mimic their interaction in the TME. In vivo, PC cells were injected subcutaneously in FPR2 WT and KO mice to study tumor progression and the immune landscape in male vs. female mice. Later, human myeloid cells were treated with FPR2 agonists and antagonists to study the interaction mechanisms in detail.

Results We found high FPR2 expression in tumor compared to healthy tissues and higher in women compared to men. In mice and human, FPR2+ myeloid cells were associated with immune cold-exclusive and cold-ignored tumor phenotype in women and men, respectively. Notably, analysis in PC and other gastrointestinal (GI)-tract cancers revealed a significant association of FPR2 expression and poor survival only in women, emerging the potential impact of sex factors in the TME. Such sexual dimorphism in the TME was associated with T cell exhaustion apparent by high expression of TIM3 and PD1. In vitro, FPR2-agonist treated myeloid-suppressive cells induced TIM3 and PD1 expression in T cells specifically in female T cells. However, a significant repression of TIM3 and a trend of PD1 expression was observed in T cells when interacting with FPR2-inhibited or -deficient myeloid cells. Finally, tumor progression was significantly slower in FPR2 KO female mice compared to WT and male FPR2 WT and KO mice.

Conclusions In this study, we have shown that sex differences are involved in shaping the TME in PC, where sexual dimorphism is still a largely unknown area allowing novel personalized/sex-specific immunotherapies. We found that FPR2 is highly involved in T cell exhaustion and can potentially be a therapeutic target for immunotherapy in women developing PC and other GI-tract cancers.

Ethics Approval The study was approved by the regional ethics review board in Stockholm (Dnr2020-06587 and Dnr2013.977-31.1) and the Swedish Board of Agriculture and regional ethical committee (10681-2020).

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.885>