Background} Paired immunoglobulin-like receptor B (PIRB), the murine ortholog of human leukocyte immunoglobulin-like receptor B 2 and 3 (LILRB2/3), is an inhibitory receptor expressed on the surface of macrophages, granulocytes, dendritic cells and B lymphocytes, in which it down-regulates their principal functions. The peculiarity of this protein is the presence of three intracellular Immunoreceptor Tyrosine-based Inhibitory Motives, able to recruit Src homology 2 domain-containing protein tyrosine phosphatases (SHP-1/2) when the receptor is activated by contacting its principal ligands, major histocompatibility complex class I molecules. Previous studies have underlined how PIRB loss is associated with i) the presence of hypersensitive B cells, which display a higher production of antibodies, ii) increased cytotoxic T cells and iii) less suppressive myeloid cells polarized toward an M1-like antitumoral phenotype. In the light of this, we wanted to better characterize extrinsic role of PIRB in modulating the antitumoral immune response in mouse models of pancreatic ductal adenocarcinoma (PDA), as well as the intrinsic role.

Methods} To this, mice lacking PIRB gene (Pirb−/−) were crossed with genetically engineered mice (GEM) that spontaneously develop pancreatic cancer. Histological and immunohistochemical analyses of pancreatic tissues were performed to measure tumor lesions and characterize the immune infiltrate. To investigate the ability to mount a memory response, OVA-expressing PDA cells were used as immunizer. ELISPOT experiment was performed to assess IFNΓ and IL17 secretion. ELISA assay was performed on sera to investigate antitumor humoral response. MTT and soft agar assay were performed to investigate proliferative and colony formation ability of wild-type and Pirb−/− PDA cell lines respectively.

Results} PIRB ablation significantly improved survival rate of GEM compared to the Pirb proficient counterpart, and this correlated with a reduced percentage of transformed ducts. Immunohistochemical analyses of pancreatic tissues demonstrated increased frequency of effector immune cells inside the tumor microenvironment. The absence of PIRB significantly delayed OVA-expressing PDA cell engraftment after immunization with OVA and increased also both antigen specific T and B cell response. Concerning the intrinsic role, in vitro experiments showed a lower proliferation rate and a lower colony formation ability by Pirb−/− PDA cell line.

Conclusions} Overall, PIRB represents a promising target to improve the antitumor immune response and deserves further characterization to design novel immunotherapy strategies for the treatment of PDA.

REFERENCES

Ethics Approval} The animal study was approved by the Italian Ministry of Health; approval number 624/2020-PR