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Regulation of PD-L1 by PPARg for immunotherapy in gastrointestinal cancers

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Objective: To investigate the role of PPARg, a drugable target of clinically approved drugs on tumor growth and immune-stimulatory features in gastrointestinal cancers (GI) and further explore the potential and promising targets that improve therapeutic efficacy, especially regarding immunotherapy in GI cancers. Methods: The expression of PPARg and PD-L1 in gastric tissues were evaluated by IHC, and the correlation with clinical characteristics was analyzed. The effect of PPARg on tumor growth and molecules expression was detected by means of Western blot, FACS and/or RT-qPCR in integrated scientific platforms comprising of human GI cancer cell lines, preclinical models (patient-derived tumor organoids, PDOs) and tissue/blood samples from healthy donors or patients. Results:
The positive rate of PPARg in epithelia of tumor tissues (31.58 %, 12/38) was significantly lower than that in normal tissues (83.33%, 5/6, **P*=0.0254). Besides, stromal PPARg expression positively correlated with PD-1 expression in tumor tissue (**P*=0.0207), and PD-1 expression was associated with lower tumor grade (**P*=0.0364), results which imply that PPARg appears to function as a potential regulator in gastric cancer both in tumor cells and the stroma microenvironment. PPARg agonists (e.g. Rosiglitazone, Pioglitazone) up-regulate PD-L1 expression in GI cancer cell lines (AGS and HT29) and CRC PDOs were found. There was an increased mRNA expression of *CD36, TFF3, ACO* and *P21* genes under higher concentrations of Rosi, which may function as target genes of PPARg agonists to trigger downstream signaling pathways in tumor cells. By contrast, PPARg agonists decrease PD-L1 and up-regulate DOK1 expression in adherent macrophages from PBMCs of healthy donors. Moreover, PD-L1 expression increases in inflammatory macrophages and is down-regulated by DOK1 was further revealed. In 3D co-cultures of PDOs and lymphokine activated killer cells (LAKs), PPARg activation enhances anti-tumor efficacy of LAKs towards PDOs under co-stimulation with IFNg, which the enhanced immunogenicity of the tumor microenvironment may account for. PD-L1 blocking Ab combined with Rosi and IFNg further decreased the overall cell viability of co-cultures, especially in PDOs with most efficiently up-regulated PD-L1 expression by Rosi, the possible reason is that the most optimal engagement between tumor cells and LAKs was established in presence of PD-L1 blocking Ab. Conclusion: A lower PPARg positive rate in epithelia of gastric tumor tissues than normal tissue indicates possible anti-tumor effects of PPARg in gastric cancer. Up-regulated PD-L1 on tumor cells and down-regulated PD-L1 on antigen-presenting cells (e.g. macrophages) upon PPARg activation may be effective to achieve tumor recognition and anti-tumor effects mediated by immune checkpoint inhibitors (ICIs). However, the exact role of PPARg, the combination of PPARg agonists and IFNg, and the molecular mechanism of anti-tumor effects induced by ICIs in GI cancers still need to be further explored with larger numbers of patients and preclinical samples.