Breakthrough: PAK1-dependent expression of PD-L1 (programmed death ligand)

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Abstract
The “Nobel-winning” monoclonal antibodies against programmed death ligand (PD-L1) or its receptor (PD-1) have been used clinically for immuno (checkpoint) therapy of cancers such as melanomas and lung cancers, but not Gemcitabine (GEM)-resistant pancreatic cancers. However, monoclonals are very expensive and are unable to pass BBB (blood brain barrier). Thus, we have been developing a series of alternative (inexpensive) chemical “checkpoint” therapeutics of small molecular weight. Some of them are among potent (highly cell-permeable and water-soluble) PAK1-blockers such as 15K (1,2,3-triazolyl ester of Ketorolac) and Frondoside A (FRA) from sea cucumber. PAK1 (RAC/CDC42-activated kinase 1) is the major oncogenic/ageing Ser/Thr kinase which is essential for both growth and metastasis of solid tumors as well as responsible for shortening the healthy lifespan as well. The major reason behind this project is based on the following hypothesis: Expression of PD-L1 depends on the oncogenic RAS-JAK-PAK1 signaling pathway. In fact, genetic silencing of PAK1 suppresses PD-L1 expression in human pancreatic cancers. Thus, it is most likely that the potent PAK1-blockers such as 15K and FRA would be inexpensive “chemical” checkpoint therapeutics for cancers including GEM-resistant pancreatic cancers. We are currently confirming this “working” hypothesis with 15K, FRA and a few other PAK1-blockers.

Background behind the hypothesis
The pioneer work on monoclonal-based immune (checkpoint) therapy of cancers by Tasuku Honjo and Jim Allison was highly recognized by 2018 Nobel Prize in physiology/ medicine. Since the checkpoint ligands such as PD-L1 (programmed death ligand) and its receptor PD-1 on cancers are responsible for their avoidance of so-called “immune surveillance” by T-cells, monoclonal antibodies against these programmed death ligands or receptors would be useful for therapy of cancers in particular melanomas and lung cancers which express these ligands or receptors at high levels [1,2]. However, so far, these monoclonals have not been successful clinically against pancreatic cancers which carry the oncogenic RAS mutant, but express PD-L1 only at low levels. 90% of pancreatic cancers are resistant to Gemcitabine (GEM), and one of the reasons for their GEM-resistance was found that GEM promotes PD-L1 expression through a Tyr-kinase family called JAK, destroying anti-tumor T-cells [3]. Since the major oncogenic/ageing Ser/Thr kinase PAK1 is activated by Tyr-kinase family called JAKs directly, we wonder if PAK1 is also responsible for RAS-JAK induced expression of PD-L1 [4]. Interestingly, PAK1 is responsible for GEM-resistance, and also for promoting T/B-cell based immune response in mice [5,6]. Thus, in theory, it is quite possible that RAS/JAK-dependent PD-L1 expression requires PAK1 as well (Figure 1). In fact, we recently confirmed that silencing PAK1 by Si RNA in pancreatic cancer cells down-regulates PD-L1 [7]. Furthermore, inhibition of MEK, a Tyr-kinase down-stream of PAK1, also down-regulates PD-L1 and is synergistic with anti-PD-L1 monoclonal to suppress the growth of colon cancers in vivo [8,9].

Accordingly, we have reached the inescapable conclusion that anti-cancer PAK1-blockers (natural or synthetic) in general could suppress PD-L1 expression in cancers including GEM-resistant pancreatic cancers. In support of this conclusion, several distinct PAK1-blockers such as triptolide, resveratrol, curcumin, melatonin and AG490 have been reported to be among PD-L1 suppressors [3,10-16]. As summarized in Figure 2, the radiation-induced PD-L1 expression in glioma cells is almost completely suppressed by AG490, a JAK inhibitor, that blocks the EGFR-RAS-JAK-PAK1-ERK signaling pathway [16]. Among the natural PAK1-blockers, so far triptolide is the most potent, suppressing the PD-L1 expression with the IC50 around 30 nM (11), by inhibiting directly both JAK and JAK, the two direct activators of PAK1 [4,17,10].

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