Efficacy of PD-1 / PD-L1 Pathway Disruptors in Syngeneic Models

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Abstract

Immune checkpoint modulators, such as antibodies targeting CTLA-4 or PD-1, are now being approved for treatment of patients with unresectable or metastatic melanoma and advanced squamous non small cell lung cancer (NSCLC) who have progressed on or after platinum-based chemotherapy. Efficacy was also evidenced on other tumor types (renal cell carcinoma, bladder, Hodgkin lymphoma, colorectal cancer (CRC)...). However, this is still needed to identify predictive biomarkers of response in order to select patients who will benefit from treatments. PD-L1 expression was proposed to be a good candidate for NSCLC, even if PD-L1 expression is a difficult parameter due to its expression on both tumor cells and immune cells as well as technical challenges to use immunohistochemical detection. The dynamic of the immune system as well as the time and where interactions between tumor cells and immune cells take place, increase the complexity of having a solid biomarker identified. In addition, for other pathologies like colorectal carcinoma, genomic biomarkers were evidenced. For example, CRC patients with mismatch repair (MMR) deficiencies have an objective response rate of 62% compared with 0% in patients with MMR-proficient tumors. Therefore, a detailed phenotype of CD8 positive T cells, tumor neoantigen expression…) will be needed to identify valuable biomarkers of response. Preliminary results using syngeneic models, both subcutaneously or orthotopically engrafted with tumors, will be evidenced. For example, CRC patients with mismatch repair (MMR) deficiencies have an objective response rate of 62% compared with 0% in patients with MMR-proficient tumors. In contrast to CTLA-4 targeting therapy, where Teff/Treg ratio was correlated to treatment efficacy, this is not the case for PD-1 or PD-L1 targeting therapies. It is hypothesized that a more complex signature (e.g. detailed phenotype of CIB positive T cells, tumor neoantigen expression…) will be needed to identify valuable biomarkers of response. Preliminary results using syngeneic models, both subcutaneously or orthotopically engrafted with tumors, will be presented.

In vivo experiments

Immune-competent mice were obtained from Charles River (France). Animals were orthotopically (OT) or subcutaneously (SC) injected with syngeneic tumor cell lines on D0. The animals received repeated injections of antibodies directed against PD-1 and/or PD-L1 at 10 mg/kg/inj. Immunocompetent mice were obtained from Charles River (France). Animals were orthotopically (OT) or subcutaneously (SC) injected with syngeneic tumor cell lines on D0. Mice were randomized based on tumor volume and treated IP with mAb against PD-1 or against PD-L1 at 10 mg/kg/inj.

Results

Mice were OT injected with 4T1 murine breast cancer cells at D0. Mice were randomized based on tumor volume and treated IP with mAb against PD-1 or against PD-L1 at 10 mg/kg/inj.

Conclusions and perspectives

Agents targeting PD-1/PD-L1 axis, alone or in combination with other molecules, may be evaluated using these syngeneic mouse models. Biomarkers of response to immune checkpoint modulators are evaluated by flow cytometry as well as immunohistochemistry analyses. Newly available RNA sequencing data will help to understand how genomics information could be used as biomarker of response for these new therapies.