PD1 B cell mimotopes with functional PD1-PDL1 blocking capacity and anti-tumor activity: New strategy for a multi-level cancer immunotherapy

Introduction and Aim

The use of immune checkpoint inhibitors (ICI) has become a major focus in cancer immunotherapy, and the application of monoclonal antibodies (mAbs) as ICIs shows impressive results in the therapy against cancers like melanoma, renal cell carcinoma or non-small cell lung cancer. Active immunization with B cell epitopes/mimotopes of ICIs rather than application of the corresponding mAbs for passive immunotherapy may, however, provide advantages such as induction of antibodies by the patient’s own immune system and overcoming the costly treatment of the mAbs. By establishing a platform, mimotopes (B cell epitopes) of the anti-human PD1 mAb Nivolumab (as an example) and of anti-mouse PD1 mAb (as a proof of principle for evaluating anti-tumor activity in vivo) were identified and characterized.

Aim: To generate ICIs mimotopes with strong capacity in inducing antibody response with anti-tumor activity.

Methods

Regenerative mimotope: Identification of mimotope Platform for identification of mimotope

T cell-based cellular assay

Synthetic mouse tumor model

BALB/c mouse grafted with mammary carcinoma cell line expressing human Her-2/neu

Results

Specifically and dose-dependently inhibit binding of Nivolumab to T cells expressing human PD1

Induce IgGs with a capacity in blocking the human PD1/PDL1 interaction (in vitro)

Mimotope of anti-mouse PD1 mAb

Passive administration of mimotope-specific IgG induces reduction of tumor progression

Active immunization with the mimotope induces reduction of tumor progression and increased level of PD1-expressing immune cells in the tumors

Summary and conclusion

By applying a syngeneic mouse model with tumors expressing human Her-2/neu, we show:

1. Anti-tumor activity by passive administration of specific IgGs against ICI mimotope, with comparable anti-tumor effect as the corresponding ICI
2. Anti-tumor activity by active immunization with mimotope of ICI

Our results may pave the way for a paradigm change for immunotherapy by active immunization with PD1 or other ICI mimotope-based vaccines against cancer, including Her-2 positive cancers. Furthermore, ICI mimotopes may also serve as adjuvants for cancer peptide-based vaccines, including Her-2/neu, thereby increasing the anti-tumor activity of the cancer vaccine.

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