Abstract

Immuno-intervention through targeting of activating and inhibitory immune checkpoints (ICPs) has shown promising results in the clinic over the last years. The entire activity spectrum of ICP modulators, used alone or in combination, is currently the subject of intense study. To facilitate this research, we developed a pipeline of human-competent mouse models expressing humanized ICP instead of their mouse counterparts, thus compounds can be tested in the absence of endogenous cross-reacting mouse targets. The humanization strategy is target-dependent but ensures that at least the entire extracellular domain is from human origin, allowing versatility for compound testing in vivo. This strategy also ensures that the biology of the target, its physiological regulation and interacting partners is preserved. Here we report the validation of the humanized CTLA4 model.

Ex vivo experiments

Normal immune cell distribution in hCTLA-4 mice suggests the presence of a functional CTLA-4

Wild-type and hCTLA-4 mice have similar tumor uptake, and survival rate in MC38 tumor model

Human CTLA-4 expression recapitulates mouse CTLA-4

Anti-tumor growth effect demonstrated in response to ipilimumab in hCTLA-4 mice

Ipiplimumab treatment increases CD8+ T cells / Treg's ratio in tumor

Suppressive function of Treg is specifically decreased in presence of anti-CTLA-4 mAb

Treatment with ipilimumab induces long-term tumor-specific immunological memory

Conclusions

These data show that CTLA4 model enables:

- Assessment of efficacy
- Mechanism of action of biologics
- Study of long-term induced immunological responses

The hCTLA4 is a novel preclinical model to evaluate therapies directed against human CTLA-4 in mice with fully functional immune systems. This model is being crossed with other ICP humanized models for assessment of zoonotic therapies and bispecific agents.