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論文審査の結果の要旨及び担当者

（申請者氏名）Ha Danbee

	（職）	氏　名
論文審査担当者		
主　査	大阪大学特任教授	坂口志文
副　査	大阪大学教授	熊ノ郷淳
副　査	大阪大学教授	竹田潔

論文審査の結果の要旨

共抑制分子CTLA-4は、がん免疫において機能的に相反するT細胞群、即ち活性化$CD8^+$ T細胞(Teff)と制御性T細胞（Treg）に発現するため、本論文では、抗CTLA-4抗体によって両者を弁別的に制御しがん免疫を増強できるか、について研究した。申請者らは、抗体依存性細胞傷害(ADCC)活性を強化した抗CTLA-4抗体を作製し、ヒト末梢血T細胞の試験管内がん抗原刺激時に同抗体を添加すれば、$CTLA\text{-}4^+$Treg、$CTLA\text{-}4^+$Teff共に除去されるが、がん抗原刺激を抗体投与から数日遅らせればTregは除去されるがTeffは除去されず、後者による免疫応答が増強される、との結果を得た。この抗体、抗原の時間差投与により、担がんマウスの腫瘍も退縮した。一方、ADCC活性を有しない抗体ではこのような抗腫瘍効果は認められなかった。本論文は、Tregと$CD8^+$T細胞の免疫学的特性に基づいた新しいがん免疫療法の可能性を示しており学位論文に値する。

論　文　内　容　の　要　旨
Synopsis of Thesis

氏　　名 Name	Ha Danbee
論文題名 Title	Differential control of human Treg and effector T cells in tumor immunity by Fc-engineered anti-CTLA-4 antibody（高ADCC活性抗ヒトCTLA-4抗体を介した制御性T細胞除去における自己・がん抗原特異的免疫反応調節）

論文内容の要旨

〔目　的(Purpose)〕

Anti-CTLA4 monoclonal antibody (mAb) is efficacious in enhancing tumor immunity in humans. CTLA-4 is expressed by conventional T cells upon activation and by naturally occurring FOXP3$^+$CD4$^+$ regulatory T (Treg) cells constitutively, raising a question of how anti-CTLA-4 mAb can differentially control these functionally opposing T-cell populations in tumor immunity.

〔方法ならびに成績(Methods/Results)〕

Here we show that FOXP3^{high} potently suppressive effector Treg cells were abundant in melanoma tissues, expressing CTLA-4 at higher levels than tumor-infiltrating CD8$^+$ T cells. Upon in vitro tumor-antigen stimulation of peripheral blood mononuclear cells from healthy individuals or melanoma patients, Fc-region-modified anti-CTLA-4 mAb with high antibody-dependent cell-mediated cytotoxicity (ADCC) and/or cellular phagocytosis (ADCP) activity selectively depleted CTLA-4$^+$FOXP3$^+$ Treg cells and consequently expanded tumor-antigen-specific CD8$^+$T cells. Importantly, the expansion occurred only when antigen stimulation was delayed several days from the antibody treatment to spare CTLA-4$^+$ activated effector CD8$^+$T cells from mAb-mediated killing. Similarly, in tumor-bearing mice, high-ADCC/ADCP anti-CTLA-4 mAb treatment with delayed tumor antigen vaccination significantly prolonged their survival and markedly elevated cytokine production by tumor-infiltrating CD8$^+$ T cells, whereas antibody treatment concurrent with vaccination did not. Anti-CTLA-4 mAb modified to exhibit a lesser or no Fc-binding activity failed to show such timing-dependent in vitro and in vivo immune enhancement.

〔総　括(Conclusion)〕

Thus, high ADCC anti-CTLA-4 mAb is able to selectively deplete effector Treg cells and evoke tumor immunity depending on the CTLA-4-expressing status of effector CD8$^+$ T cells. These findings are instrumental in designing cancer immunotherapy with mAbs targeting the molecules commonly expressed by FOXP3$^+$ Treg cells and tumor-reactive effector T cells.