様式３

論　文　内　容　の　要　旨

氏　名　（倉谷　歩見　）	
論文題名	Tumor-associated macrophages secrete Platelet factor 4 to promote Th1-Treg differentiation and suppress antitumor immunity (腫瘍関連マクロファージは Platelet factor 4 を分泌してTh1-Treg分化を促進し、抗腫瘍免疫を抑制する)

論文内容

The tumor microenvironment contains various immunosuppressive cells, including regulatory T cells (Tregs) and tumor-associated macrophages (TAMs). It has previously shown that one subset of Tregs, Th1-type Tregs (Th1-Tregs), significantly accumulates in tumors and potently suppresses antitumor immunity. However, the mechanism of Th1-Treg accumulation in tumors remained unknown. Recent studies have revealed a high correlation between TAMs and tumor-infiltrating Tregs, suggesting that TAMs may be involved in the recruitment of Tregs into tumors and in immunosuppressive functions.

In this study, I generated a novel mouse model in which TAMs can be labeled and removed to elucidate the function of TAMs. Depletion of TAMs resulted in a reduced percentage of Th1-Tregs in the tumor and suppressed tumor growth. I then examined whether TAMs are involved in the induction of differentiation of Tregs into Th1-Tregs by a TAM-Treg co-culture system. The results revealed that TAM induces Treg differentiation into Th1-Treg. Furthermore, we investigated the mechanism of TAM induction of Th1-Treg, and found that the chemokine platelet factor 4 (PF4), which is highly expressed in TAMs, is involved in Th1-Treg differentiation.

To elucidate the *in vivo* function of PF4, systemic PF4-deficient and macrophage-specific PF4-deficient mice were generated. The results showed that both systemic PF4-deficient and macrophage-specific PF4-deficient mice had a reduced percentage of Th1-Tregs in tumors and slower tumor growth compared to wild-type mice.

Finally, to investigate whether systemic neutralization of PF4 with PF4-specific antibodies has immunotherapeutic effects against tumors, neutralizing antibodies that inhibit PF4 function were generated, and administered it to tumor-bearing mice. The results showed that the administration of PF4 neutralizing antibody reduced the percentage of Th1-Tregs in the tumor, activated anti-tumor immunity, and suppressed tumor growth. Furthermore, administration of PF4-neutralizing antibody did not induce autoimmunity which occurs by removal of all Tregs.

These findings indicate that PF4 produced by TAMs promotes tumor growth by inducing Treg differentiation into Th1-Tregs and strongly suppressing anti-tumor immunity. PF4 may thus be a novel therapeutic target for safe and effective cancer immunotherapy.

様式 7

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本論文は、腫瘍内微小環境（TME）における新たな腫瘍免疫抑制機構を明らかにした論文である。具体的に、Th1型制御性T細胞（Th1-Treg）がTMEに高度に蓄積するメカニズムを探索し、それに腫瘍付随マクロファージ(TAM)が関与することを突き止めた。さらにTAMから放出されるケモカインの一つである血小板第４因子(PF4)がTh1-Tregを誘導し、またPF4を全身性またはマクロファージ特異的に欠損させることによって腫瘍内Th1-Tregの減少と腫瘍サイズの増大を抑制できた。またPF4に対する中和抗体を作製し、担がんマウスに投与することによってPF4欠損マウスと同様に、腫瘍内Th1-Tregの減少と腫瘍サイズの増大を抑制し、抗腫瘍免疫を活性化できたことから、PF4を標的とした新規のがん免疫療法を提唱することができた。以上の研究内容は内外から高く評価され、Science誌で公表され、公聴会においても問題なく発表されたことから、博士の学位を授与するに値するものと認める。なお、チェックツール“iThenticate 2.0”を使用し、剽窃、引用漏れ、二重投稿等のチェックを終えていることを申し添える。