氏名	石　軍
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学位授与の要件	医歯薬学総合研究科病態制御科学専攻 （学位規則第４条第１項該当）
学位論文題目	Identification of CD123$^+$ myeloid dendritic cells as an early-stage immature subset with strong tumoristatic potential （腫瘍増殖抑制活性を持つCD123陽性未熟骨髄系樹状細胞の同定）
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学位論文内容の要旨

CD123 has been identified as a specific surface marker for plasmacytoid dendritic cells (PDCs). However, CD123 has recently been shown to be expressed on freshly isolated or in vitro generated myeloid dendritic cells (MDCs). In this article, we investigated whether expression of CD123 on monocyte-derived MDCs was related to their function, especially to tumor-inhibiting potential. MDCs were induced from cord blood CD14$^+$ monocytes with granulocyte-macrophage colony-stimulating factor (800IU/ml) and interleukine-4 (1000IU/ml) for 7 days, and then CD123$^+$ cells were isolated by immunomagnetic selection. We observed that CD123$^+$ cells represented the major subset on day7 of the culture, with co-expression of CD11c determined by flow cytometry. They lost CD14 expression, and exhibited higher levels of CD86 costimulatory molecules, and lower level of HLA-DR and human DC specific marker CD1a than CD123$^-$ fraction. However, neither CD123$^+$ nor CD123$^-$ population expressed detectable levels of maturation-specific marker CD83. CD123$^+$ MDCs were smaller than CD123$^-$ MDCs detected by scanning electron microscopy, while the short and thick projections on CD123$^+$ MDCs were similar to those on the negative fraction. CD123$^+$MDCs exerted more significant endocytosis and less T-cell stimulating activity than CD123$^-$MDCs which are often referred to as typical MDCs. Meanwhile, CD123$^+$ MDCs exhibited more significant anti-proliferative activity toward hematological tumor cell lines of U937 and Jurkat even at a low effector:target ratio measured by a 24h ^{3}H-TdR uptake assay. CD123$^+$ MDCs expressed higher level of cytoplasmic TNF-α-related apoptosis-inducing ligand (TRAIL), but no detectable surface TRAIL and very little soluble TRAIL. Pretreatment with recombinant human TRAIL-R2:Fc fusion protein significantly reduced the tumor-inhibiting effect of CD123$^+$ MDCs, whereas the effect of CD123$^-$ MDCs was slightly blocked. Overall, our data demonstrated that CD123$^+$ MDCs were an early-stage immature DC subset, with a significant tumor-inhibiting activity partially through enhanced cytoplasmic TRAIL.

論文審査結果の要旨

本研究は、臍帯血単球を用いて、骨髄性樹状細胞（MDC）のサブポピュレーションであるCD123陽性細胞と陰性細胞について、その表現型および機能について解析したものである。その結果、両者で、細胞表面抗原であるCD1a、HLA-DR、CD83、CD86の発現には有意な差はなかったが、貪食能は、CD123$^+$MDCの方がCD123$^-$MDCよりも優れていた。同種リンパ球混合培養では、CD123$^-$MDCの方がCD123$^+$MDCよりも強い刺激能を示した。さらに、CD123$^+$MDCにより強い抗腫瘍活性を認め、この効果はTRAILを介するものであることが示唆された。これらの結果は、CD123$^+$MDCはCD123$^-$MDCに比べて、より未分化なMDCであることを示している。これはMDC分化について重要な知見であり、価値ある業績であると認める。よって、本研究者は博士（医学）の学位を得る資格があると認める。