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氏名	村尾綾子（むらお あやこ）
博士の専攻分野の名称	博士（医学）
学位記番号	第　２３６３４　号
学位授与年月日	平成22年３月23日
学位授与の要件	学位規則第４条第１項該当 医学系研究科内科系臨床医学専攻
学位論文名	High frequencies of less differentiated and more proliferative WT1-specific CD8$^+$T cells in bone marrow in tumor-bearing patients : An important role of bone marrow as a secondary lymphoid organ （固形癌患者の骨髄には未分化で分裂可能なWT1-specific CD8$^+$T cellが高頻度に存在する）
論文審査委員	（主査） 教授　川瀬　一郎 （副査） 教授　金倉　譲　　教授　青笹　克之

論文内容の要旨

In tumor-bearing patients, tumor-associated antigens (TAAs)-specific cytotoxic T lymphocytes (CTLs) are spontaneously induced as a result of immune response to TAAs and play an important role in anti-tumor immunity. WT1 (Wilms' tumor gene 1) is overexpressed in various types of tumor and WT1 protein is a promising pan-TAA because of its high immunogenicity. In this study, to clarify the immune response to the WT1 antigen, WT1-specific CD8$^+$ T cells that were spontaneously induced in patients with solid tumor were comparatively analyzed in both bone marrow (BM) and peripheral blood (PB). WT1-specific CD8$^+$ T cells more frequently existed in BM than in PB, while frequencies of naïve (CCR7$^+$ CD45RA$^+$), central memory (CCR7$^+$CD45RA$^-$), effector-memory (CCR7$^-$ CD45RA$^-$), and effector (CCR7$^-$ CD45RA$^+$) subsets were not significantly different between BM and PB. However, analysis of these subsets for the expression of CD57 and CD28, which were associated with differentiation, revealed that effector-memory and effector subsets of the WT1-specific CD8$^+$ T cells in BM had less differentiated phenotypes and more proliferative potential than those in PB. Furthermore, CD107a/b functional assay for WT1 peptide-specific cytotoxic potential and CFSE dilution assay for WT1 peptide-specific proliferation also showed that WT1-specific CD8$^+$ T cells in BM were less cytotoxic and more proliferative in response to WT1 peptide than those in PB. These results implied that BM played an important role as a secondary lymphoid organ in tumor-bearing patients. Preferential residence of WT1-specific CD8$^+$ T cells in BM could be at least in part explained by higher expression of chemokine receptor CCR5, whose ligand was expressed on BM fibroblasts, on the WT1-specific CD8$^+$ T cells in BM, compared to those in PB. These results should provide us with an insight into WT1-specific immune response in tumor-bearing patients and give us an idea of enhancement of clinical response in WT1 protein-targeted immunotherapy.

論文審査の結果の要旨

Wilms' tumor gene 1 (WT1)は様々な癌で高発現しており、癌遺伝子としての機能を持っている。この研究では固形癌患者における骨髄中のWT1-specific Cytotoxic T lymphocytes (CTLs)の詳細な解析を行うため、末梢血中のWT1-specific CTLsと比較することを目的とした。

WT1テトラマーを用いたフローサイトメトリーによる解析から、骨髄中のWT1-specific CTLsの頻度は末梢血中のものより有意に高いということが明らかになった。また、WT1-specific CTLsのCCR7とCD45RAによる分化活性化の度合いを評価するphenotype解析では骨髄と末梢血で差は見られなかった。しかし、CD57とCD28を加えた詳細な解析では、骨髄中のWT1-specific CTLsは末梢血のものよりも未分化であることが明らかになった。

更に、WT1-specific CTLsの機能解析ではWT1特異的増殖能は骨髄のものが有意に高く、WT1特異的細胞傷害活性は骨髄のものが有意に低かった。

骨髄は、未分化であるが増殖能があるWT1-specific CTLsがプールされている、いわば二次リンパ節のような機能を持つことが示唆された。

これらの内容は、博士の学位授与に値する。