

学 位 論 文 要 旨

博士課程 甲・乙	第 号	氏 名	Yanuar Rahmat Fauzi
<p>[論文題名]</p> <p>Antitumor effects of chloroquine/hydroxychloroquine mediated by inhibition of the NF-κB signaling pathway through abrogation of autophagic p47 degradation in adult T-cell leukemia/lymphoma cells</p> <p>成人 T 細胞白血病リンパ腫細胞におけるオートファジーによる p47 タンパク質分解の抑制と NF-κB 情報伝達阻害を介したクロロキン/ヒドロキシクロロキンの抗腫瘍効果 (PLOS ONE, accepted)</p> <p>[要 旨]</p> <p>Adult T-cell leukemia/lymphoma (ATLL) originates from human T-cell leukemia virus type 1 (HTLV-1) infection due to the activation of the nuclear factor-κB (NF-κB) signaling pathway to maintain proliferation and survival. An important mechanism of the activated NF-κB signaling pathway in ATLL is the activation of the macroautophagy-lysosomal degradation of p47, a negative regulator of the NF-κB pathway. Therefore, we considered the use of chloroquine (CQ) or hydroxychloroquine (HCQ) (CQ/HCQ) as an autophagy inhibitor to treat ATLL; these drugs were well known FDA approved as antimalarial drugs for decades. In this paper, I investigated the therapeutic efficacy of CQ/HCQ, as NF-κB inhibitors, in ATLL mediated by blockade of p47 degradation. Administration of CQ/HCQ to ATLL cell lines and primary ATLL cells induced cell growth inhibition in a dose-dependent manner, and the majority of cells underwent apoptosis after CQ administration. As to the molecular mechanism, autophagy was inhibited in CQ-treated ATLL cells, and activation of the NF-κB pathway was suppressed with the restoration of the p47 level. When the antitumor effect of CQ/HCQ was examined using immunodeficient mice transplanted with ATLL cell lines, CQ/HCQ significantly suppressed tumor growth and improved the survival rate in the ATLL xenograft mouse model. Importantly, HCQ selectively induced ATLL cell death in the ATLL xenograft mouse model at the dose used to treat SLE. Taken together, my study suggest that the inhibition of autophagy by CQ/HCQ may become a novel and effective strategy for the treatment of ATLL.</p>			

備考 論文要旨は、和文にあつては 2, 000 字程度、英文にあつては 1, 200 語程度