

## Identification of chloroquine/hydroxychloroquine as candidate therapeutic agents for adult T-cell leukemia/lymphoma

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### Background:

Nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling pathway plays a pivotal role in the survival and proliferation of adult T-cell leukemia/lymphoma (ATLL) cells. We previously reported the mechanism by which p47 (NSFL1C), a negative regulator of the NF- $\kappa$ B pathway, is degraded by the autophagy-lysosomal pathway, resulting in constitutive activation of the NF- $\kappa$ B pathway (Sci Rep. 2019). Since chloroquine (CQ) or hydroxychloroquine (HCQ) were recently reported to inhibit autophagy, and CQ/HCQ are used for malaria and autoimmune diseases including systemic lupus erythematosus (SLE), we investigated their efficacy on ATLL cells.

### Methods:

Antitumor effects of CQ/HCQ were studied *in vitro* and *in vivo* mouse models. The administration of HCQ was performed orally as in the case of clinical usage.

### Results:

Administration of CQ/HCQ to ATLL cell lines and primary ATLL cells induced cell growth inhibition in a dose-dependent manner. On the other hand, normal peripheral blood mononuclear cells were less sensitive to CQ/HCQ. Moreover, in all the ATLL cell lines tested, more than 80% of the cells caused apoptosis 24 hours after CQ/HCQ administration. As its molecular mechanism, autophagy

was inhibited in ATLL cells treated with CQ/HCQ, and activation of the NF- $\kappa$ B pathway was suppressed with increases in p47 and I $\kappa$ B $\alpha$  levels. Next, the antitumor effect of CQ/HCQ was examined using immunodeficient mice subcutaneously transplanted with ATLL cell lines. The administration of CQ/HCQ significantly suppressed tumor growth. In addition, in an intravenous injection of ATLL cell line to mice, a significant prolongation of survival in the HCQ group was observed. More importantly, HCQ was found to almost completely suppress the growth of ATLL cell lines at the same dose used in the clinical setting of SLE.

**Conclusion:** CQ/HCQ may be effective as anti-ATLL drugs, and the clinical significance of the development of therapeutic agents by drug repositioning of CQ/HCQ is considered to be great.

**Disclosure of Interest Statement:**

None

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