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Low concentrations of chloroquine and 3-methyladenine suppress the viability of retinoblastoma cells synergistically with Vincristine independent of autophagy inhibition

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Background & Aim: To study the inhibition of retinoblastoma cell viability by two commonly used autophagy inhibitors, chloroquine (CQ) and 3-methyladenine (3-MA), alone or in combination with the conventional chemotherapeutic drug vincristine (VCR) and to investigate whether the mechanisms of these drugs are related to inhibition of autophagy.

Methods: On retinoblastoma cell line HXO-Rb44, VCR, CQ and 3-MA were used individually or combined. The cell viability was determined by CCK8 method and the cellular autophagic activity was determined by Western blotting of LC3 and p62. Caspase 3 fragmentation and Akt activation was also determined by Western blotting.

Results: VCR induced cell cycle arrest and apoptosis in HXORb44 cells, but only inhibited autophagy at relatively high doses. Both CQ and 3-MA were synergistic with VCR to inhibit the growth of retinoblastoma cells and the combinational use significantly reduced the dosage of each drug. The lowest effective dose of CQ and 3-MA was most efficient to add on VCR; however, such dose was not sufficient to suppress autophagy in these cells. CQ could directly induce caspase activation, while 3-MA significantly inhibited Akt phosphorylation.

Conclusion: CQ and 3-MA were synergistic with VCR to inhibit retinoblastoma cells. Our result suggested a novel strategy to combine CQ or 3-MA with VCR to reduce the side effects of each drug. However, lack of change in the autophagic activity when using the two drugs at lower doses suggests multiple mechanisms of action of the same drug at different doses. At higher doses, the drugs could inhibit autophagy, while at lower doses; they suppress tumor growth via autophagy-independent mechanisms.

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