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## Superiority of anti-cancer drugs whose efficacy increases under acidic conditions

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Although blood and tissues are usually maintained at pH around 7.4 in mammals, the extracellular pH drops below 6.5 in solid cancer nests. Such acidic environments may decrease intracellular pH and disrupt cellular functions mediated by a large number of enzymes with pH sensitive catalytic activity. Target molecules of anti-cancer drugs are largely enzymes whose activity is dependent on pH, suggesting that the efficacy of anti-cancer drugs varies as pH changes. We have measured the inhibitory effect of over 270 well-known compounds on cancer cell proliferation in media of pH 7.5 and 6.7, and five compounds, lovastatin, cantharidin, manumycin A, doxorubicin, and ionomycin, showed high inhibition at pH 6.7, but their inhibitory effects were low at pH 7.5. We further examined the inhibitory mechanism of statins and found that the inhibition was caused by the decrease in protein geranylgeranylation. Clinical investigations have revealed the therapeutic effect of statins on cancer patients. It can be argued that the anti-cancer drugs with high efficacy under acidic conditions have low side effects on cells in normal tissues, especially immune cells in blood, because normal tissues and blood are generally slightly alkaline. In fact, statins are now prescribed for the treatment of hyperlipidemia with low side effects. These results suggested that the screening of anti-cancer compounds in acidic medium would be useful for development of new anti-cancer chemotherapeutics.

### Biography

Hiroshi Kobayashi has completed his PhD (1974) in Biochemistry from University of Tokyo in Japan. After his Postdoctoral training at Colorado University Medical Center in USA, he started to study adaptation strategies of microorganisms to acidic environments at Chiba University in 1978. His recent research is focused on mammalian cell functions under acidic conditions from 1996 at Graduate School of Pharmaceutical Sciences, Chiba University. He retired in March 2012 and continues his research as a Professor Emeritus at Chiba University. He has published more than 20 papers in reputed journals during the recent 10 years.

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