Hiroshi Kobayashi, Madridge J Cancer Stud Res. 2016
http://dx.doi.org/10.18689/2640-5180.a1.002

madridge CONFERENCES

International
Cancer Study & Therapy Conference

April 4-6, 2016 Baltimore, USA

Superiority of anti-cancer drugs specific to acidic cancer nests

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Solid cancer nests are acidified below pH 6.5, although normal tissues and blood are usually maintained at pH around 7.4 in mammals. Such acidification of cancer nests may change the efficacy of anti-cancer drugs when their target molecules are enzymes whose activity is dependent on pH. We measured the inhibitory effect of approximately 300 compounds at pH 6.7 and 7.5, and five compounds, lovastatin, cantharidin, manumycin A, doxorubicin, and ionomycin, showed a high activity to inhibit cancer cell proliferation at pH 6.7, while their inhibitory effect was very low at pH 7.5. We focused our work on statins because clinical investigations had already revealed the therapeutic effect of statins on human cancers. It has been reported recently that statins inhibit cancer growth in mice. Statins have been used as a drug against hyperlipidemia because statins inhibit cholesterol synthesis and no effect on cancer cell proliferation had been reported in vitro until our study. Our further investigations have revealed that the inhibition of cell proliferation by statins is caused by the decrease in the synthesis of geranylgeranyl diphosphate used for protein prenylation but not in cholesterol synthesis. Statins are generally accepted to be a safe drug without serious side effects, such as immune system dysfunction. Our data showed that the inhibitory effect of statins on immune cells is negligible in medium whose pH is close to blood pH. These results suggest that anti-cancer drugs specific to acidic areas are useful for cancer chemotherapy with low side effects. We found that the expression of approximately 700 genes was elevated at acidic pH, suggesting that many other anti-cancer drugs whose efficacy increases in acidic cancer nests could be found besides statins. Our in vitro assay method may promote exploitation of new anti-cancer drugs specific to acidic areas, which improves cancer chemotherapy.

Biography:

Hiroshi Kobayashi received his Ph.D. in Biochemistry from University of Tokyo in 1974. After his postdoctoral training at Colorado University Medical Center, 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 is now Professor Emeritus at Chiba University. He works as an associate editor of International Immunopharmacology published by Elsevier B.V. from 2014.