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Target genes for acidosis-dependent anti-cancer drugs

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While mammalian blood and normal tissues are usually maintained at pH around 7.4, the extracellular pH drops below 6.5 in solid cancer nests. Enzymes which function preferentially at acidic pH may be the target molecules of anti-cancer drugs. Our group have found that the inhibition of protein prenylation attenuates proliferation of cancer cells at acidic pH, suggesting that an enzyme(s) to prenylate proteins is functioning under acidic conditions. In addition to the enzyme for protein prenylation, there may be other enzymes functioning under acidic conditions. To find such enzymes, the expression of 24,000 genes was examined using a DNA array chip in mesothelioma cells, and the expression of approximately 700 genes was elevated at acidic pH. The elevated expression of these genes was found in other cancer cells grown under acidic conditions and in human specimens from cancer patients. These results suggest that mammalian cells have many enzymes which function preferentially in acidic cancer nests, and that drugs inhibiting these enzymes could be potent candidates for anti-cancer chemotherapeutics with less side-effect, especially on immune systems in blood and normal tissues, because acidosis-dependent drugs are expected to be less effective in tissues whose pH is alkaline. In fact, inhibitors of protein prenylation had little effect on proliferation and cytokine production of immune cells at alkaline pH. The screening under acidic conditions may be a useful way to find new anti-cancer drugs which are effective in acidic cancer nests.

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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