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Generation and use of genetically modified human cell lines: A promising approach for in vitro toxicology studies

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Abstract

A series of genetically modified cells should be useful to investigate the effect/cytotoxicity of clinically useful drugs, environmental chemicals, nanomaterials, or plant compounds. Human gene-knockout cells, created by gene targeting via homologous recombination, are otherwise isogenic and thus will provide invaluable information, which, unlike that from model organisms, is readily applicable to human medicine and drug development. In general, gene targeting in human somatic cells is too inefficient to routinely generate gene-knockout cells. However, we have recently reported that a human pre-B cell line, Nalm-6, allows exceptionally efficient gene targeting (average efficiency: 1-5%). Even more intriguingly, we found that the targeting efficiency can be elevated to 25-100% with the use of exon-trap vectors. Using this high-efficiency gene-targeting system, we have created quite a few human mutant cell lines, most of which lack a gene(s) implicated in repair of damaged DNA. As such, we generated cells deficient in DNA ligase IV and confirmed that this critical ligase for non-homologous end-joining is responsible for most (though not all) random integration events, a major or perhaps the sole obstacle to gene-targeting experiments. More importantly, it should be mentioned that the DNA ligase IV-deficient cells were extremely sensitive to topoisomerase II inhibitors such as etoposide, while these cells showed tolerance to the topoisomerase I inhibitor camptothecin. This work, along with our additional studies, unequivocally suggests usefulness of isogenic human cell lines in in vitro toxicology studies aimed at assessing and analyzing the cytotoxicity of drugs or compounds of interest.

Biography

Noritaka Adachi graduated from the University of Tokyo in 1994. Since then, he has been working for Yokohama City University, and is now a professor at Yokohama City University. He has published more than 60 papers in reputed journals, including Cell and PNAS. Invited Editorial Board Member for the Journal of Gene Technology.