THE DEVELOPMENT OF ANTI-TUBERCULOSIS GENE DRUG INDUCING AUTOPHAGY AND ACTIVATION OF MACROPHAGE

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Tuberculosis, which is caused by Mycobacterium tuberculosis (MTB), is one of the most frequently occurring infections in the world. MTB is an intracellular parasitic bacterium that mainly infects the respiratory tract and hides in alveolar macrophages (AMs). Recently, it was reported that induction of autophagy in macrophages eliminates MTB\(^1\). In this study, we tried to develop a gene drug for inducing autophagy and activating macrophages. The genes, which related to autophagy and macrophage activation were first cloned by PCR and recombined into the expression vector (CAT7 neo). Each gene was then transfected to mouse macrophage cell line, RAW267.4 by using an Amaya system. After introducing genes, the effects of these gene drug candidates were examined. The induction of autophagy in macrophages and activation of macrophages by some of our gene drugs were confirmed by fluorescent microscopic observation and western blot analysis. Based on these findings, it was shown that the gene drugs were effective for MTB. At present, the side effects such as inflammation by introducing gene drugs into macrophages are being estimated and the other candidates for gene drugs which induce autophagy and activation of macrophages are being screened.


EVALUATION OF DRUG-INDUCED HEPATOTOXICITY USING CHIMERIC PXB-MICE\(^\text{®}\) WITH HIGHLY HUMANIZED LIVER

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[Purpose] In order to evaluate drug-induced liver injury (DILI) in humans, we have analyzed changes in hepatic gene expression in rats and chimera PXB-mice\(^\text{®}\) with highly humanized liver using 31 different hepatotoxics and non-hepatotocicants.

[Methods] Oral treatment with hepatotoxicants and non-hepatotoxicants was applied to rats and PXB-mice\(^\text{®}\) three-times daily at high doses (ca. 20% of reported LD50), followed by hepatic total RNA preparation and gene expression analyses using oligonucleotide microarray chips. Several maker gene candidates, which specifically responded to the hepatotoxicants, were extracted and further evaluated by using a score method in which DILI prediction score for each drug is calculated from marker gene expression levels and weight factors optimized by least-squares fitting.

[Results and Discussion] In the predictive model construction, one-by-one omit analyses revealed that PXB-mice\(^\text{®}\) gave better predictability of drug-induced hepatotoxicity as compared with rats. Hepatotoxics which are not involved in the construction of the predictive model, were also judged as hepatotoxic successfully.

[Conclusions] PXB-mice\(^\text{®}\) have a potential to bridge the gap between rodent-type and human-type livers and to explain the difference of in vivo and in vitro response of human hepatocytes against hepatotoxics.