Further works

We have developed several screening and testing methods with medaka for evaluating the hormonal activity of natural steroid hormones and endocrine disrupting chemicals (EDCs). Although the developed screening and testing methods are applicable to estrogen and androgen agonists, the applicability of the test methods for their antagonist are unknown. Therefore, we need to verify the applicability of the methods to the antagonists. Furthermore, we should investigate the usablity of the test methods for weak EDCs, although it has been demonstrated in some test methods. Hereafter, we need to study in order to choose the test method that is the best in terms of sensitivity and cost effectiveness. So far we understand that partial life-cycle test is sensitive compared to reproduction test in both points of general toxicity and endocrine disruption. However, some chemicals may display more toxicity to the next generation than the parent. We also have to consider the differences in susceptibility to chemicals between medaka and other fish and/or organisms. In this point of view, the mechanism causing the different susceptibility to chemicals between two generations and among organisms should be studied out.

A number of works may be necessary for the demonstration of those. However, recent biotechnological tools may help and accelerate to resolve the matter in question. Furthermore, it is not clarified that how relevant the change observed in such endpoints as secondary sex characteristics, gonadal histology, VTG and so on is involved in the ecological effects based on endpoints like survival, growth and reproduction. Therefore, we need to discuss and consider how to evaluate the change of these endpoints and how to use the results obtained by the developed test methods.

In vitro studies also have been developed in order to screen many of the chemicals of concern. As part of studies, we found that species difference in the receptor binding affinity shows importance of the differences in sensitivities to chemicals among diverse species to assess the endocrine disrupting effects of chemicals to ecosystem. In conclusion, we should clarify this issue by receptor binding assay using various fish estrogen receptors.

In this report, the sex-determinating gene of medaka, DMY (Y-specific DM-domain gene) and fish sexual differentiation are discussed. This gene is the first to be found in non-mammalian vertebrates. We have much effort on the area of the DNA chip containing a series of genes associated with the sexual differentiation in **medaka**. A series of genes associated with regulating the sexual differentiation have been cloned and prepared to develop a DNA macro array. The results of these studies with utilizing the gene technology will be useful to make clear the effects of EDCs on the mechanism of sexual differentiation in **medaka** and also the species difference in sensitivities.