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Influence of xenoestrogens on metabolism of medaka testosterone
メダカ･テストステロン代謝に与える外因性エストロゲンの影響

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Certain environmental xenobiotics disrupt growth development, maturation and reproduction of fish by modulation of endocrine system. The extent of disruption is often dependent upon the growth stage when the organism is originally exposed. In our laboratory we have investigated xenoestrogenic effects on Japanese medaka (*Oryzias latipes*). Induction of vitellogenin in the adult male and inhibition of reproduction and hatching at environmentally relevant chemical concentrations have been reported. The hormone like effects of these compounds are thought to be mediated by numerous mechanisms of action. Our laboratory has investigating modification of steroid biosynthesis and metabolism as one possible mechanism of endocrine disruption. To know the biological mechanism of medaka testosterone metabolism through development is significant for understanding endocrine disruption on fish. To address this issue we are investigating two major metabolic enzymes associated with hormone metabolism in medaka liver. We have previously identified two isoforms of CYP3A (CYP3A 38 and 3A40) and have demonstrated both age dependence expression and metabolic activity for both genes. Comparison of CYP3A38 and 40 genes sequences indicate that they share 90% sequence similarity with 141 nucleotide substitutions coding for 49 amino acid differences. Putative identification of CYP3A substrate recognition site (SRS) 1-6 indicate that 12 of the 49 amino acid differences between CYP3A38 and 40 occur in SRS regions associated with steroid hydroxylation. Heterologous expression of 3A38 and 40 demonstrated different metabolic activity toward testosterone. CYP3A38 showed catalytic activities for the 6β-hydroxylation and the 16β-hydroxylation of testosterone, 3A40 showed for the 6β-hydroxylation. When adult male medaka was exposed to 17β-estradiol, the expression of both CYP3A isoforms was completely inhibited. Testosterone metabolism in medaka liver microsome was also reduced. This presentation will discuss new target of xenoestrogen by modulation of testosterone in teleost development.