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選択された号の論文の4件中1～4を表示しています

**Original Article**

### Cadmium inhibits forskolin-induced differentiation of human placental BeWo cells

Shoko Ogushi, Tsuyoshi Nakanishi, Tomoki Kimura

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Cadmium (Cd) is an environmental pollutant. Blood Cd levels in pregnant women have been associated with premature births, infant birth size, placenta previa, and placenta accreta. There have been concerns on the reproductive developmental toxicity of Cd. The choriocarcinoma cell line BeWo, a cellular *in vitro* model for studying syncytial fusion, has been widely used to study the reproductive and developmental toxic effects of pollutants. Here, we examine the inhibitory effect of Cd against forskolin (FSK)-induced BeWo differentiation. Results showed that Cd exposure inhibited the FSK-induced expression of syncytiotrophoblast-related genes LGALS13, ERVFRD1, SDC1, and CGB3. Inhibition of LGALS13 expression was due to the inhibition of the PKA pathway, whereas the inhibition of the other three genes could be due to the inhibition of the other pathways. These findings could help clarify the reproductive and developmental toxicity of Cd.



**Original Article**

### Constitutive expression of cytochrome P450 1B1 endows testicular Leydig cells with susceptibility to 7,12-dimethylbenzanthracene-induced cell death

Yoon-Jae Kim, Ji-Eun Park, Jin-Yong Chung, Ji Young Kim, Seung Gee Lee ...

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Testicular Leydig cells produce testosterone through the participation of steroidogenic proteins. The CYP1B1 enzyme has been shown to catalyze 7,12-dimethylbenzanthracene (DMBA), a representative polycyclic aromatic hydrocarbon. We hypothesized that exposure to DMBA causes Leydig cell cytotoxicity through activation of CYP1B1. Leydig cells were exposed to various concentrations of DMBA for the induction of CYP1B1 expression and activity. The status of CYP1B1 function was monitored by evaluation of cytotoxicity-mediated cell death. Our data show that exposure to DMBA causes cytotoxicity in Leydig cells by CYP1B1 activation. DMBA evoked a significant increase in the generation of reactive oxygen species (ROS) by which the depolarization of mitochondrial membrane potential (MMP) is initiated and caspase-3 activation is augmented. The knockdown of CYP1B1 expression resulted in the suppression of DMBA-induced apoptosis via reduced p53 activation and caspase-3 activation, suggesting that a final metabolite of DMBA (i.e., DMBA-DE) bioactivated by CYP1B1 induces p53 activation by binding to DNA and subsequently causing apoptosis via caspase-3 activation. This finding provides evidence for constitutive expression of CYP1B1 in Leydig cells, which is a trait that only requires an initiating signal for its activity. Further research on CYP1B1 activation-provoked steroid metabolism in Leydig cells may provide decisive clues for elucidating its innate function.

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**Original Article**

## Fetal loss due to Th1-skewed Th1/Th2 balance with increase (not decrease) of regulatory T cells in abortion-prone mouse model

Miho Sakakibara, Yosuke Maeda, Kazuichi Nakamura

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We used an abortion-prone mouse model, generated by mating female CBA/J mice with male DBA/2JJcl mice, to examine the effects of changes in the Th1/Th2 cell ratio and the percentage of regulatory T (Treg) cells on the maintenance of pregnancy. We subcutaneously injected female CBA/J mice once each with 50 μg/mouse of *Dermatophagoides farinae* (Df) extract and the squalene-based adjuvant (SquA); 10 days later, these mice were mated with male DBA/2JJcl mice. Compared with injection of vehicle or adjuvant, the Df treatment decreased the Th1/Th2 cell ratio and concomitantly increased the percentage of Treg cells in the spleen. In addition, fetal death rates were decreased. We then explored a substance which shifted the Th1/Th2 balance toward Th1 side. We found that 50 μg/mouse of keyhole limpet hemocyanin (KLH) increased the splenic Th1/Th2 cell ratio of nonpregnant

female CBA/J mice. We subcutaneously injected female CBA/J mice with KLH and SquA; 10 days later, these mice were mated with male DBA/2JJcl mice. Compared with injection of vehicle or adjuvant, treatment with KLH enhanced the Th1 bias during pregnancy and increased the fetal death rate. The percentage of Treg cells, however, was increased in these KLH-injected pregnant mice contrary to our presumption. All collected data showed strong positive correlation between the Th1/Th2 cell ratio and fetal death rate. The increase in Treg cells independent of effects on the fetal death rate suggests that Treg cells do not necessarily induce maternal tolerance to the fetus but may prevent excessive Th1/Th2 imbalance during pregnancy.

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**Original Article**

## CREB is a potential marker associated with drug-induced liver injury: Identification and validation through transcriptome database analysis

Qiyue Zhang, Shiori Taniguchi, Kanako So, Masahiro Tsuda, Yuriko Higuc ...

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Drug-induced liver injury (DILI) is the main cause of failure in drug development and postapproval withdrawal. Although toxicogenomic techniques provide an unprecedented opportunity for mechanistic assessment and biomarker discovery, they are not suitable for the screening of large numbers of exploratory compounds in early drug discovery. Using a comprehensive analysis of toxicogenomics (TGx) data, we aimed to find DILI-relevant transcription factors (TFs) that could be incorporated into a reporter gene assay system. Gene set enrichment analysis (GSEA) of the Open TG-GATEs dataset highlighted 4 DILI-relevant TFs, including CREB, NRF2, ELK-1, and E2F. Using ten drugs with already assigned idiosyncratic toxicity (IDT) risks, reporter gene assays were conducted in HepG2 cells in the presence of the S9 mix. There were weak correlations between NRF2 activity and IDT risk, whereas strong correlations were observed between CREB activity and IDT risk. In addition, CREB activation associated with 3 Withdrawn/Black box Warning drugs was reversed by pretreatment with a PKA inhibitor. Collectively, we suggest that CREB might be a sensitive biomarker for DILI prediction, and its response to stress induced by high-risk drugs might be primarily regulated by the PKA/CREB signaling pathway.

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