Adverse Outcome Pathway (AOP) development on Wnt/beta-catenin signaling pathway related to cancer

Shihori Tanabe[1], Kazuhiko Aoyagi[2], Sabina Quader[3], Horacio Cabral[4], Ryuichi Ono[5], Akihiko Hirose[1], Hiroshi Yokozaki[6], Hiroki Sasaki[7]

[1]Div. Risk Assessment, Biol. Safety Res. Center, Natl. Inst. Health Sci., [2]Dept. Clin. Genomics, Natl. Cancer Center Res. Inst., [3]iCONM, [4]Grad. Sch. Engineer., Tokyo Univ., [5]Div. Cel. Mol. Toxicol., Biol. Safety Res. Center, Natl. Inst. Health Sci., [6]Dept. Pathol., Grad. Sch. Med., Kobe Univ., [7]Dept. Transl. Oncol., Natl. Cancer Center Res. Inst.

Adverse Outcome Pathway (AOP) is developed for the prediction of the adverse effects. Epithelial-mesenchymal transition (EMT) plays an important role in the acquisition of cancer stem cell (CSC) feature and drug resistance, which are main hallmarks of cancer malignancy. Although previous findings have shown that Wnt/beta-catenin signaling pathway is activated in the cancer progression, the precise mechanism of Wnt/beta-catenin signaling in EMT and CSCs are not fully understood. To reveal the network pathways in EMT, gene expression in mesenchymal stem cells (MSCs) and diffuse-type gastric cancer (GC) as well as intestinal-type GC have been analyzed and compared. The network pathways in MSCs and GC were analyzed with Ingenuity Pathway Analysis (IPA). The gene expression profiling demonstrated that gene expression of cadherin 1 (*CDH1*), Wnt family member 9A (*WNT9A*) and catenin beta 1 (*CTNNB1*) were up-regulated in diffuse-type GC compared to MSCs. The gene expression of growth factor receptor bound protein 7 (*GRB7*) and erb-b2 receptor tyrosine kinase 2 (*ERBB2*) were up-regulated in intestinal-type GC compared to diffuse-type GC. Wnt/beta-catenin signaling, as well as ERBB signaling networks, involved in EMT, CSCs and drug resistance, have been investigated and profiled in bioinformatics. In conclusion, the Wnt/beta-catenin signaling pathway was included in EMT-related molecular network pathways in MSCs and GC, which may contribute into the elucidation of mechanism in the drug resistance of CSC population. AOP related to Wnt/beta-catenin signaling pathway is discussed.