

### S04-3 **The role and mechanism of changes in zinc transporters expression in cellular cadmium transport**

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We have previously shown that the mRNA level of slc39a8 (ZIP8) was decreased in metallothionein (MT)-null Cd-resistant cells. However, the mechanism of down-regulation of ZIP8 has not yet been clarified. We found that the CpG island of slc39a8 gene was hypermethylated by using methylation-specific PCR assay. Treatment of Cd-resistant cells with 5-aza-2'-deoxycytidine, which inhibit DNA methyltransferase, resulted in recovery of mRNA and protein levels of ZIP8 leading to the increases in Cd accumulation and sensitivity. These results suggest that epigenetic regulation may be involved in the down-regulation of slc39a8 gene in Cd-resistant cells.

We also established Cd-resistant cells from MT-expressing mouse cells. Although MT expression is enhanced, accumulation of Cd was decreased in these Cd-resistant cells. Expressions of several transport systems including ZIP8 and some Ca channels were reduced in Cd-resistant cells. Cross-resistance to MnCl<sub>2</sub> suggests the change in the transport system involved in both Cd and Mn accumulation. Thus, in addition to a high expression of MT, the changes in transport systems involved in Cd, Mn and Zn may play important roles in acquisition of Cd resistance. The roles of several transporters and Ca channels, the expression of which was changed in Cd-resistant cells, in Cd, Mn and Zn transport were now under investigation.