

Metallothionein Regulation and Menkes' Disease

Studies of the regulation of metallothionein synthesis have provided insight concerning the molecular basis of human genetic diseases. Several serious human diseases involve altered copper metabolism. One of these, Menkes' disease, is an inherited disorder linked to the X chromosome in which copper is distributed throughout the body in an abnormal fashion. Some tissues, such as the intestine and kidney, accumulate abnormally large amounts of copper. Other tissues, such as those in blood vessels and brain, lack adequate amounts of copper. The results of this metabolic disorder are neural degeneration, abnormal vasculature, and early death.

A clue to the molecular basis for this disease came from studies at Los Alamos and elsewhere of cells isolated from patients with Menkes' disease. These cells accumulate more copper than do normal cells when exposed to typical physiological levels of the metal. Copper is one of the metals whose ions bind to metallothionein. Moreover, high levels of copper bound to metallothionein correlated with enhanced

cellular copper uptake and retention in Menkes' cells. Thus, in Menkes' cells, the synthesis of metallothionein appears to be "locked on," that is, in the constitutive mode. The disease apparently involves, not genetically altered MT genes, but altered regulation of gene expression for metallothionein.

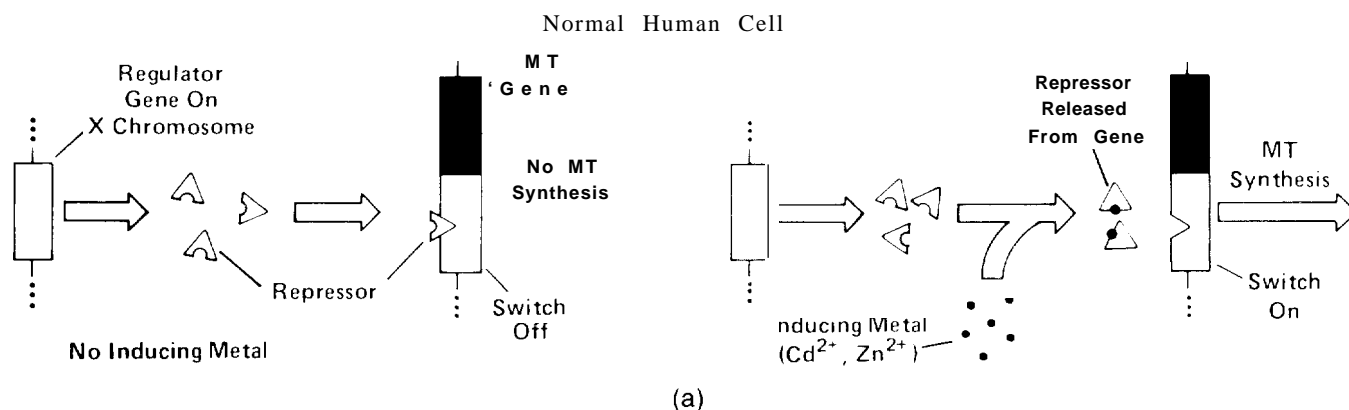
Although Menkes' disease is inherited as a recessive X-linked trait, the MT gene is not on the X chromosome. This observation suggests that there is a gene on the X chromosome encoding a molecule that regulates copper uptake and, perhaps, MT gene expression (see part (a) of the figure). This latter gene is apparently the one altered in Menkes' cells so that an effective regulator is not synthesized (b).

To explore this idea further, we used somatic cell genetic techniques to fuse normal hamster and Menkes' human cells, creating hybrid cells with the genetic components of both species. The MT gene from the hamster cells was inactive (due to methylation) so that it could not be induced to synthesize hamster metallothionein (c). However, copper uptake and the synthesis of

human metallothionein were found to be normal in the hybrid cells.

One hypothesis is that the hybrid cells now contained a nondefective gene on the X chromosome of the hamster cell that encoded the regulator. The hamster regulator was synthesized in the hybrid cells, interacted in the usual fashion with the appropriate metal ions, and then regulated the synthesis of the human gene for metallothionein normally (d). Once human metallothionein gene expression was controlled, the cell could maintain normal levels of copper ions. Alternatively, by correcting the abnormal copper uptake in Menkes' cells, the hybrid cells may have regained normal basal levels of metallothionein synthesis.

These results suggest that the regulator is actually a repressor of MT gene activity, because without a regulator, the synthesis of metallothionein is always turned on. The results also demonstrate that inter-species regulation of metallothionein synthesis is possible, an exciting result that further points out the evolutionary conservation of the metallothionein system. ■



(a) A model for the normal regulation of metallothionein synthesis. Normal human cells control the synthesis of metallothionein with a regulator whose gene is located on the X chromosome. The regulator acts as a repressor in that metal

ions induce synthesis of metallothionein by causing the repressor to leave the switch region adjacent to the MT gene, turning the switch on.