Expression of the galectin-1 (L-14-I) gene, elevated in most differentiated and transformed cell lines, has been studied in cell hybrid systems. Fusion of L-14-I nonproducing rat liver differentiated FAO cells with dedifferentiated rat liver BRL3A cells leads to extinction of liver-specific gene expression while L-14-I mRNA levels remain high. Interspecific hybrids produced by fusion of tumorigenic human osteosarcoma 143TK- with FAO cells show loss of both differentiated functions and tumorigenic phenotype and activation of the FAO L-14-I alleles. Increased expression of rat L-14-I alleles was also observed in human osteosarcoma x rat thyroid cells transient heterokaryons. The data presented here show that expression of the L-14-I gene is subject to dominant positive control and that it correlates with loss of differentiation-specific functions, but it is independent from tumorigenicity. L-14-I activation in FAO cells is achieved by treatment with 5-azacytidine. This result suggests that DNA demethylation is responsible or a prerequisite for L-14-I activation in hybrids.