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The role of imprint instability in human cancer

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The development of cancer in humans is not only caused by genetic lesions (mutations, deletions, translocations etc.) but also by epigenetic aberrations. One epigenetic phenomenon whose deregulation contributes to the development and progression of cancer in humans is imprinting, the parent-of-origin specific expression of genes. A causal role of imprinting aberrations in human carcinogenesis is suggested by several human disorders, e.g., complete parthenogenesis in ovarian teratomas and androgenic conception in hydatidiform moles. Contribution of imprinting defects in cancer is best exemplified in patients with Beckwith-Wiedemann Syndrome (BWS) which is associated with a high risk of cancer compared to the general population. Since some genes demonstrate developmental stage-specific or tissue specific imprinting, the study of imprinting can be complicated and the comparison of results from different studies might be misleading. The use of proper controls for the identification of imprint alterations is of uppermost importance. These experimental challenges might be the reason why much less is known about imprinting defects in human cancer compared to aberrant promoter hypermethylation of tumor suppressor genes. Based on published information about validated imprinted genes, genome-wide expression and DNA methylation data, and results obtained with primary human patient samples (and not cell lines or animal models!), we started to identify deregulation of imprinted genes in breast and liver cancer and study the functional relevance of these findings. As documented in several publications from our group, we could show that deregulation of imprinted loci is an underappreciated but widespread phenomenon with clinical relevance. We could also show difficulty to identify switches in allelic expression are much more frequent than thought before and that deregulation of the only quite recently identified imprinting of the well-known tumor suppressor gene RB1 is a frequent event in liver cancer.