DNA Methylation Differences in Tumors of Mice and Men

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Tumor development depends on a combination of both genetic and epigenetic changes. In order to study human cancer biology, genetically engineered mouse models (GEMMs) of cancer are derived from either overexpressing oncogenes or silencing tumor suppressors. Few studies have examined epigenetic changes in these mouse models. Importantly, GEMMs are used to study the preclinical efficacy of drugs. "It is an all but too common story to hear of a compound that showed great promise when tested in a mouse model of cancer only to fail when tested in patients," according to Dr. Scott Diede in the Clinical Research Division. A new study published in *Epigenetics* from Dr. Diede in the laboratory of Dr. Stephen Tapscott (Human Biology Division) suggests one possible reason for this low success rate: mouse models of cancer are fundamentally different with respect to DNA methylation compared to human tumor samples.

One common epigenetic change found in tumors is the addition of methyl groups on cytosine bases of DNA located in gene promoters. DNA hypermethylation at these locations turns off the expression of genes. In a previous study, Dr. Diede and colleagues found extensive DNA methylation changes in human medulloblastoma patient samples that altered expression of genes in critical developmental pathways (Diede *et al*., 2009). To determine if these epigenetic changes were also found in three different GEMMs of medulloblastoma, Dr. Diede and colleagues examined DNA methylation patterns across the genome for both human and mouse brain tumors compared to normal brain tissue. In human tumors, 121 loci had strong promoter DNA methylation (greater than 60% more methylated than normal cerebellum), while the mouse models exhibited this level of hypermethylation in only 0 to 16 loci. When the researchers lowered the stringency of methylation to greater than 33% methylated, 315 additional hypermethylated promoters were found for the human tumors compared to only 7 to 70 for the three medulloblastoma GEMMs.

The researchers then asked whether this decreased DNA methylation pattern was found in other mouse models of cancer. Compared to human tumors or cancer cell lines, GEMMs of Burkitt lymphoma and breast cancer also displayed less promoter DNA hypermethylation. Diede *et al*. then asked if mouse cells are capable of acquiring extensive promoter DNA hypermethylation by

examining mouse fibroblasts that spontaneously immortalize under extensive culture. The immortalized mouse cells indeed acquired DNA hypermethylation, a phenomenon that is also observed in human fibroblasts, suggesting that DNA hypermethylation may contribute to bypassing cell senescence in initiating tumor development. However, the researchers hypothesize that this event is not required for tumorigenesis in the GEMMs of cancer, at least not the five GEMMs driven by overexpressing oncogenes examined in this study.

"Our results suggest caution when using GEMMs of cancer as preclinical platforms for therapy development, especially for those drugs that alter epigenetic modifications such as DNA methylation," according to Dr. Diede. "We hope to be able to use this new information to better understand human cancer and develop more faithful mouse models to help identify therapies to increase cure rates for patients with cancer."

Diede SJ, Yao Z, Keyes CC, Tyler AE, Dey J, Hackett CS, Elsaesser K, Kemp CJ, Neiman PE, Weiss WA, Olson JM, Tapscott SJ. 2013. Fundamental differences in promoter CpG island DNA hypermethylation between human cancer and genetically engineered mouse models of cancer. *Epigenetics*. Epub ahead of print, doi:10.4161/epi.26486.

See also: Diede SJ, Guenthoer J, Geng LN, Mahoney SE, Marotta M, Olson JM, Tanaka H, Tapscott SJ. 2009. DNA methylation of developmental genes in pediatric medulloblastomas identified by denaturation analysis of methylation differences.*Proceedings of the National Academy of Science* USA 107:234-239.

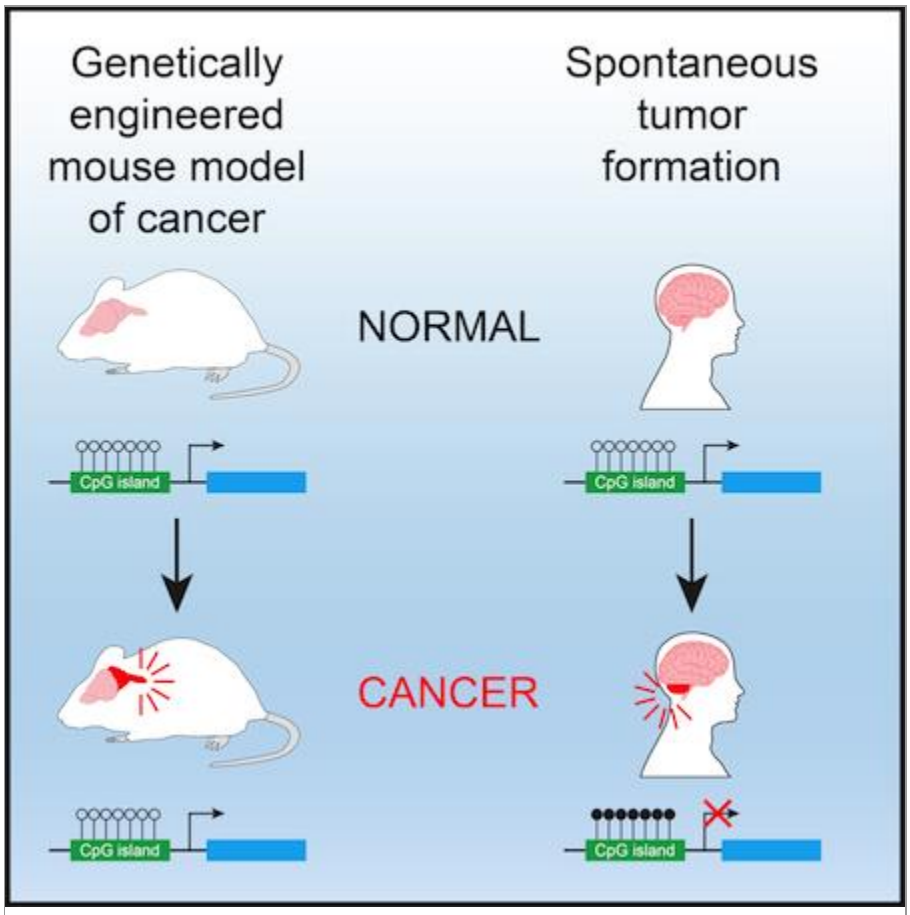

Image provided by Dr. Scott Diede

DNA methylation patterns differ between genetically engineered mouse models of cancer and primary human cancers, including medulloblastomas. breast cancer and Burkitt lymphoma.