Hoffman Lab

About Hoffman Lab

The Hoffman Lab studies various aspects of epigenetics, including genomic imprinting and its aberrations, and the role of long-range chromatin interactions in the regulation of gene expression.

The imprinted insulin-like growth factor II gene (*IGF2*) is expressed only from the paternal allele in a tissue-specific, promoter-specific, and development-specific manner. Dysregulation of *IGF2* imprinting is a hallmark of many human tumors, including Wilms' tumors and colorectal cancers, resulting in biallelic *IGF2* expression and, potentially, abnormally high IGF-II peptide production. When over-expressed, this mitogenic peptide may promote tumor growth via autocrine and/or paracrine interactions. Loss of imprinting (LOI) is thought to be among the earliest and most common epigenetic changes in cancer. We have hypothesized that aberrant *IGF2* imprinting in tumors is caused by loss of *trans* imprinting factor(s) and/or altered epigenetic modifications of *cis* elements in designated imprinting control regions. We are testing this hypothesis in an innovative model in which abnormal *IGF2* imprinting in tumor cells can be corrected or normalized by "epigenetic reprogramming" by exposing tumor cells to a cellular micro-environment where *IGF2* imprinting is maintained. We have been particularly interested in the role of CTCF and the PRC2 complex in the maintenance of genomic imprinting.

Recently it has become clear that nuclear architecture and chromatin geography are important factors in the regulation of gene expression, and that these components may play a vital epigenetic role both in normal physiology as well as in the initiation and progression of malignancies. In inter-mitotic cells, chromosomes decondense into a 3-dimensional "chromosome territory" within an organized nuclear architecture. Loops of chromatin physically unite genes on different chromosomes, allowing co-regulated genes to co-localize within the nucleus. We have shown that the genes *Nf1* (on mouse chromosome 11) and *Igf2* (on chromosome 7) physically interact, modulating each other's transcription. We suggest that it is those genes whose proteins act in concert in metabolic or signal transduction pathways which migrate to a common chromatin hub, thereby synchronizing or modulating their transcription.

A central paradigm of medical genetics is that the phenotype of a deletion syndrome results from the disruption of the deleted genes themselves. However, the function of the deleted genes often does not explain either the phenotype of the syndrome or the variation among individuals with the same genetic lesion. The human genome project provided us with a linear sequence, inadvertently inspiring a "flat genome" paradigm, where genetic diseases are investigated in the context of a linear genome. In direct contradistinction to this dogma, we propose that genetic diseases can be caused or modified by changes in physical, long-range interactions that normally occur between loci that are now deleted and genes that are far from the deleted region when plotted on a linear genetic map.

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