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Epigenetics and Gene Expression
November 2016

Epigenetic Mechanisms in Disease States

Genetic diseases provide excellent opportunities to study genetic and epigenetic regulatory mechanisms and how they interact for one of two reasons. First, genetic diseases either overexpress or underexpress key factors, as in the case of many cancers. Second, they provide a living version of a knockout when a mutation occurs in the DNA itself, allowing us to observe what changes when a gene is absent or unregulated and infer its pathway interactions from there. Studies done on such disease states, particularly in instances of cancer, have seen a surge of new information come out around transcription regulation mechanisms.

DNA methylation, the covalent addition of a methyl group to a cytosine or adenine residue (only cytosine in mammals), is regulated by DNA methyltransferase 1 (DNMT1). Though it can have both downregulating and upregulating effects on gene products, methylation itself is inhibitory. Dysregulation of DNMT1 can cause inappropriate methylation of genes involved in cell cycle checkpoints, which is one aspect seen in cancers. Indeed, specific patterns have been observed in cancerous cells, whereby DNA exhibits global hypomethylation and local hypermethylation at genes that control cell growth and tumor suppression. Studying the effects of knockdowns of certain genes, such as p53, has revealed valuable information on the DNMT1mechanism. Together with SP1, p53 inhibits DNMT1 in lung cancer and results in greater DNMT expression. However, upregulation of SP1 changes the interaction and causes SP1 to be a DNMT1 activator. Additional cancer studies have also shown the notable regulatory effect that miRNAs can have, as in the instance of miR-21, a major dysregulated micro RNA overexpressed in many cancers and whose role is to regulate major tumor suppressor genes PTEN and PDCD. A study of esophageal cancer showed that in addition to mutations in the STAT3 gene, zinc deficiency can also cause miR-21 overpexpression.

Cancer studies are useful for illustrating how multiple genetic and epigenetic regulatory mechanisms may affect one product or pathway. A breast cancer study subjected EZH2, a H3K27 methyltransferase overexpressed in many solid tumor cancers, to RNAi therapy to silence it, finding that tumor growth diminished. It is known that EZH2 inhibits the tumor suppressor RUNX3, and when EZH2 is overexpressed, RUNX3 levels decrease, which in turn decreases CDK-inhibitor p21which regulates the kinases required for cell growth, resulting in unchecked cell growth. Most interestingly, RUNX3 is hypermethylated in cancer cells, but when EZH2 is reduced, RUNX3 expression increases, suggesting that it is also regulated by histone methylation at H3K27.

RNAi has also begun to be studied for its involvement in epigenetic regulation, where it may also play a role in disease proliferation. Research speculates that cancer cells may exploit the body's RNAi mechanism to sustain expression of genes necessary for growth because the human Argonaute protein, AGO1, has interactions with thousands of promoters and transcribed genes which are mostly positive for gene expression and which are affected by altering miRNA genesis.

The more we know about these mechanisms in disease states, the more progress is made in developing therapies that target not the phenotypic manifestations of disease but their genetic root cause. Lentiviral-mediated RNAi therapy is being explored as a novel treatment for ovarian cancer and many diseases that involve the overexpression of certain genes and/or proteins due to its silencing mechanisms. Some diseases, such as Duchenne muscula dystrophy (DMD), which is caused by a premature stop codon in the dystrophin protein, could also benefit from RNAi-based treatments as

RNA regulates alternative splicing. Like RNAi, epigenetic silencing has been examined as a potential cancer therapy, specifically by reprogramming cancer cells not to methylate promoters at tumor suppressors in genes, as in the example of CXCL9 and CXCL10 which express chemokines in ovarian cancer cells. Finally, DNA methylation can be used marker for disease presence and prognosis, as in the case of GSTP1, a gene methylated in prostate cancer.