AUTHOR COMMENTARIES - From Special Topics

Epigenetics - March 2009
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Randy Jirtle

From the Special Topic of Epigenetics

One of the key papers in our Special Topics Research Front Map on Epigenetic Gene Regulation is "Transposable elements: targets for early nutritional effects on epigenetic gene regulation" (Waterland, R.A. and Jirtle, R.L., Mol. Cell. Biol*. 23[15]: 5293-300, August 2003). In* Essential Science Indicators℠ *from Thomson Reuters, this paper is currently a Highly Cited Paper in the field of Molecular Biology & Genetics, with 306 citations up to April 30, 2009.*

This paper was coauthored Dr. Randy Jirtle and Dr. Robert Waterland, who was a postdoctoral fellow Dr. Jirtle's at the time. Dr. Jirtle's record in our database includes 56 papers cited a total of 2,466 times between January 1, 1999 and April 30, 2009. He is the Director of the Epigenetics and Imprinting Laboratory at Duke University in Durham, NC.

In the interview below, ScienceWatch.com *talks with Dr. Jirtle about this paper and its influence on the field of epigenetics.*

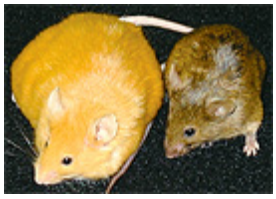
SW: Would you please describe the significance of your paper and why it is highly cited?

Both animal experiments and human epidemiological studies demonstrate that maternal nutritional privation during pregnancy is adversely associated with an offspring's susceptibility to diseases and neurological disorders after birth. Our 2003 *Molecular and Cellular Biology* paper provided the first experimental evidence that the memory system linking these two disparate time points in life involves epigenetic modifications established soon after fertilization1. In so doing, we opened the mechanistic 'black box' of the developmental origins of adult disease susceptibility, and firmly placed the word, *epigenetics*, in the vernacular of this research field.

Specifically, we showed that dietary supplementation of viable yellow agouti (Avy) mice during pregnancy with methyl donors (i.e. choline, betaine, folic acid, and vitamin B12) decreased the incidence of offspring with a yellow coat color (Figure 1), which is associated concomitantly with a reduction in their risk of developing obesity, diabetes, and cancer. Moreover, these phenotypic changes were shown to result from increased DNA methylation of a transposable element upstream of the *Agouti* gene rather than mutation of the gene.

Interestingly, genistein, a weak phytoestrogen found in soy products, elicits a similar epigenetic effect at the *Avy* locus even though it is not a methyl donor[2]. Both methyl donors and genistein can also counteract the CpG hypomethylation caused by bisphenol A, an endocrine disrupting agent used to make hard clear plastic and epoxy resins[3]. As Hippocrates asserted over two millennia ago, food is medicine!

Figure 1 [+] details



Effects of nutrition on the epigenome of viable yellow agouti (Avy) mice... [+] details

SW: How did you become involved in this research, and were there any particular successes or obstacles that stand out?

Our lab became involved in epigenetics research in the early 1990s when we identified the *IGF2R (Insulin-like Growth Factor 2 Receptor)* to be a liver tumor suppressor gene[4]. *IGF2R* is also imprinted in a number of species[5], and the paternal-specific allelic silencing that results in monoallelic expression of this gene is epigenetically controlled. Thus, *IGF2R* was the first imprinted tumor suppressor gene identified.

With this discovery, we realized that cancer could potentially arise by a single genetic mutation or a lone epigenetic event in an imprinted tumor suppressor gene. But, could changes in the environment during pregnancy cause modifications at epigenetically labile loci that increase the risk of developing cancer and other complex diseases years later? We used the Avy mouse model described above to address this fundamentally important question.

SW: Where do you see your research and the broader field leading in the future?

The number of papers published last year on epigenetics was 16,000—a 40-fold increase since we started research in this field. Therefore, epigenetics research is growing exponentially. This is due, in part, to the availability of high-throughput sequencing platforms that have enabled scientists to ascertain how DNA methylation, histone marks, nucleosome position, and non-coding RNA species interact at the chromatin level to control cell differentiation and normal cell function. As these regulatory systems are more precisely defined, we will increasingly focus our laboratory research efforts on identifying those genes that are imprinted in humans, and determining their role in the pathogenesis of human conditions, *e.g.,* autism, bipolar disorder, cancer, drug addiction, and schizophrenia.

SW: What are the implications of your work for this field?

"Despite the immense popularity and ease of using mice to 'model' human diseases, it appears they may not be a suitable choice for studying diseases resulting principally from the epigenetic deregulation of imprinted genes, or for assessing human risk from environmental factors that

The publication of our 2003 *Molecular and Cellular Biology* paper demonstrated unequivocally that the risk of developing diseases in later life can result from environmental interference of normal epigenetic programming during gestation[1]. As a consequence, it is clear that variation not only in the genome, but also the epigenome participates in complex disease formation.

Genomic imprinting evolved about 180 million years ago in an ancestor common to placental mammals (Therians), and it resulted in some genes having the same parental allele always epigenetically silenced[6]. Imprinted genes are particularly susceptible to epigenetic deregulation because the unique imprint marks that control their idiosyncratic functional haploid state must staunchly be maintained when the epigenome is normally reset after fertilization[7]. Thus, imprinted genes are candidate disease susceptibility loci uniquely vulnerable to environmentally induced deregulation during early development.

With the use of computer-learning algorithms, we recently predicted the presence of 600 candidate imprinted genes in mice[8]; but only 156 in humans[9]. Not only are humans predicted to have fewer imprinted genes than mice, but there is also only a 30% overlap between their imprinted gene repertoires. Despite the immense popularity and ease of using mice to 'model' human diseases, it appears they may not be a suitable choice for studying diseases resulting principally from the epigenetic deregulation of imprinted genes, or for assessing human risk from environmental factors that alter the epigenome rather than mutate the genome.

Thus, we are entering a new era of biological research—one where it is becoming increasingly apparent that humans are indeed the best model for understanding diseases afflicting mankind, as stated so prophetically by the English poet Alexander Pope in the early 18th century. This important realization, and the change in the research approach to which it points, will require scientists from numerous disciplines to collaborate in order to bring together the biological samples and patients and

alter the epigenome rather than mutate the genome"

exposure information needed to tease out the alterations in our epigenome, which link environmental exposures during susceptible stages of life to disease formation years later. The field of medicine could potentially be revolutionized by this epigenetic perspective of disease formation—subsequently shifting our healthcare emphasis from therapy to prevention.

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Figure 1:

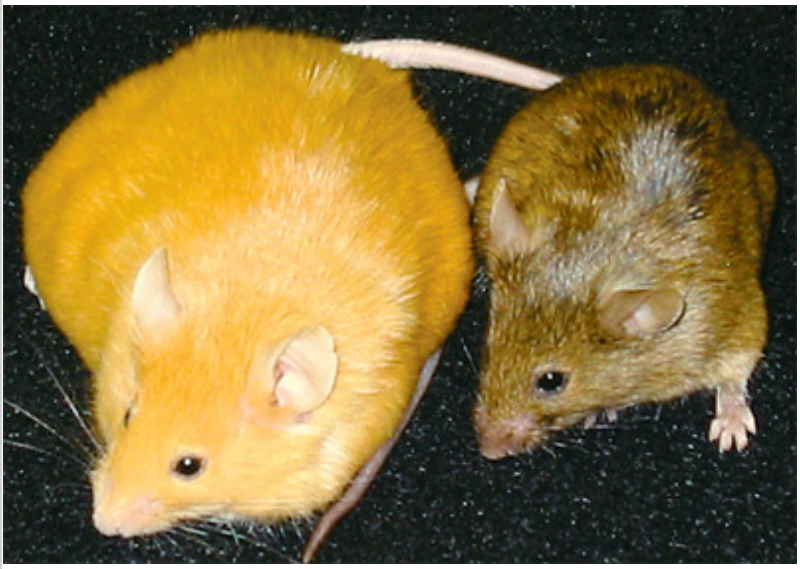

Figure 1:

Effects of nutrition on the epigenome of viable yellow agouti (Avy) mice. These female one year old Avy mice are isogenic. The mother of the mouse on the left ate a normal mouse diet while pregnant. In contrast, the mother of the mouse on the right ate a diet supplemented with methyl donors while pregnant [1]. The marked differences in the coat color and weight of these offspring resulted from a dissimilarity in

the level of DNA methylation at the Agouti locus.

Randy Jirtle's current most-cited paper in *Essential Science Indicators*, with 306 cites:

Waterland RA, Jirtle RL, "Transposable elements: Targets for early nutritional effects on epigenetic gene regulation," *Mol. Cell Biol*. 23(15): 5293-300, August 2003. Source: *Essential Science Indicators* from Thomson Reuters.

KEYWORDS: MATERNAL METHYL SUPPLEMENTS; MOUSE AGOUTI LOCUS; DNA METHYLATION; CYTOSINE METHYLATION; MICE; EXPRESSION; INHERITANCE; MAMMALS, ADULT DISEASE SUSCEPTIBILITY, MATERNAL NUTRITIONAL PRIVATION, TRANSPOSABLE ELEMENT; EPIGENETICS; GESTATION; GENOMIC IMPRINTING.

PDF

back to top

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