NATURE VS. NURTURE and Beyond

Heredity in the Post-Darwin Era

Continued from cover.

Longtime Darwinists have abandoned the genomic road and sought higher ground from which to view inheritance. Why the sudden course correction and affinity for altitude? The answer: the massive, international undertaking known as the Human Genome Project was successfully completed in 2003, but failed to meet expectations. What should have been the "whole story" was instead only the prologue. Researchers had hoped to find genes responsible for diabetes and other inherited diseases, but found only coding for the predisposition to these diseases. Also unanswered in the 20,000-gene sequencing was the riddle of genetically identical twins with disparate medical histories. The explanation for these anomalies was observed from on high — within the epigenome, or the layer "above the genome."

The tenet of epigenetics is the overarching idea that people inherit more than their genes. A discussion topic in the 1970s, this scientific discipline ceded the spotlight to the genetics frenzy, until recently. Epigenetics describes the process by which organisms modulate their gene expression in response to the environment. Offers Duke University oncologist, Randy Jirtle: "If you think of the genome as being like … the hardware of the computer, [then] the epigenome would be like the software that tells the computer when, how and how much to work." The "software" effectively transmits information from one generation to another, without updating the DNA structural hardware.

The Nuts and Bolts

There are currently four known forms of epigenetic variation, one of which – chromatin markers – is generating a great deal of publishing buzz. These chemical tags work to control gene expression via the modification of chromatin, the coiled complex of DNA and proteins that packages the genetic material in the cell nucleus. Epigenetic changes to the chromatin are manifested by the addition or removal of chemical tags on either of the proteins, known as histones, or the DNA itself.

Methyl groups, configurations of one carbon atom bonded to three hydrogen atoms – are abundantly occurring tags that attach directly to DNA nucleotides during embryonic development. This biochemical process – DNA methylation – adds this CH3 group to either a carbon atom in the 5-position of the cytosine pyrimidine ring (CpG islands) or a nitrogen atom in the 6-position of the adenine purine ring. [Cytosine and adenine are two of the four bases, or building blocks, of DNA.] Methyltransferase enzymes catalyze the reaction that alters the structure of the chromatin, but leaves the DNA sequence untouched. Once a cytosine base is methylated, copies of the base will also be methylated.

There are hundreds of different methylation reactions that occur in biological systems; 60 to 90% of all CpG sites are methylated. At the 5-position, methylation serves to suppress gene expression in vertebrates. Research shows that inappropriate gene silencing as a result of hypermethylation influences "virtually every step in tumor progression." And, in breast cancer metastases, epigenetic alterations in methylation and histone patterns conspire with genetic mutations to promote life-threatening changes in gene expression and create genomic instability.

Epigenetic marks also play a role in cell differentiation. They are part of the mechanism that instructs two genetically identical cells, in utero, to become entirely different organs. Epigenetic changes can also be inherited. Environmental stressors can change the methylation patterns of an entire population, altering the characteristics of generations of offspring long-removed from the environment of their forbearers. And, say epigeneticists, all of this can occur via the simple addition of a methyl group to a receptive carbon atom.

Early Inquiry and Darwin in the Rear View

In the 1980s, Dr. Lars Olov Bygren studied the long-term effects that years of feast and famine had on the tiny 19th century population of Norbotton, Sweden. He traced the lineage of 99 residents born in 1905 to ascertain the amount of food that was available to their grandparents when they were young. He wondered if the early childhood experience of the parent could alter the traits of their children.

With the help of historical agricultural data, Bygren found that boys, who had food aplenty in their youth, produced sons and grandsons who lived shorter lives (six years on average) than the grandsons of boys who endured hunger. Once Bygren's team controlled for socioeconomic variables, the difference in longevity grew to a whopping 32 years. Similar results were found for grandmothers and their female offspring.

Well, wait just a Darwinian minute here … evolutionary changes take place over millions of years of natural selection, right? Darwin and the genetic community had completely dismissed the earlier claims of Jean-Baptiste Lamarck, who suggested that evolution could occur in just a generation or two. Bygren's burgeoning hypothesis supported the contentions of another (former) committed Darwinist, Dr. Marcus Pembrey. In a seminal paper, Pembray argued that humans, at the genetic level, were working overtime to adapt to the swift-paced social and environmental changes of the modern era. Reasoning that the time frame was too abbreviated for Darwinian selection, Pembray set out to demonstrate that a second form of coding was responsible. The two scientists, with the help of epidemiologist Jean Golding, followed thousands of young people and their parents (before kids). Their study produced a wealth of insight, including: the sons of men who smoked before puberty were at higher risk for adult obesity; high maternal anxiety during

pregnancy correlated with childhood asthma; and kids who were kept too clean were more likely to develop eczema. All of this data served to tip the heredity scale in support of nurture over nature.

Meanwhile, Back in the Lab

Working in the new era of epigenetic acceptance, Duke University oncologist Randy Jirtle experimented (2003) with genetically identical mice to demonstrate the role of DNA methylation in the alteration of an organism's phenotype (expressed trait). Using the agouti gene, which codes for yellow fur and a propensity for obesity and diabetes, Jirtle's team fed one group of pregnant agouti mice a B vitamin-rich diet and withheld prenatal nutrition from a second. Acting as methyl donors, the B vitamins increased the frequency of methylation and enhanced the expression of the agouti gene. Without touching a whisker of the rodents' DNA structure, the researchers induced mothers to produce healthy, brown pups without a predisposition for diabetes.

Similarly, Moshe Szyf, working in Montreal, showed that rats "whose mothers groom and lick them when they are young grow up to be much calmer than rats whose mothers neglected them." Rather than credit good ol' childrearing, Szyf found that the nurturing mothers activated a gene that suppressed the creation of cortisol, a stress-causing hormone. Without the activation of the gene, the love-starved pups produced more cortisol and were more anxious.

Late last year, researchers at Stanford University observed that mutations in several chromatin regulators can extend the life span of roundworms by up to 30 percent. The study suggests "that transgenerational inheritance of longevity does occur in roundworms via modulations of [three key] proteins," says Dr. Anne Brunet. "We hypothesize that when the parental generation is missing key components that normally regulate chromatin, epigenetic marks are not completely reset from one generation to the next in the germ line, thereby inducing heritable changes in gene expression." Humans possess similar proteins that, in time, could potentially grant future generations some extended life span "wiggle" room.

Way Cool

Until recently, epigenome-based changes were studied in the lab and/or over a relatively few generations. With the 2012 discovery of 26,000-year-old bison bones in the DNA-preserving permafrost of Canada, Australian palaeobiologist Alan Cooper saw an opportunity to test "the evolutional role of epigenetic variation and inheritance … on an evolutionary time scale."

Cooper extracted DNA samples from six fossilized *Bos taurus*, only one of which was suitable for amplification. After dating the DNA using accelerator mass spectrometry, his team established two controls: DNA from a 20-year-old mummified cattle skin and from fresh bovine decay.

Researchers uncovered cytosine methylation patterns using bisulphite sequencing. This method converts all nonmethylated cytosines into uracil, essentially destroying all but the methylated versions. Much to their delight, the team found not only ancient methylated DNA, but also methylations that, for the most part, occurred at the same sites in the modern cattle samples. According to Cooper, these findings suggest that epigenetic changes can facilitate a rapid adaptive process in response to catastrophic climate change. In other words, evolution waits for no man … not even Darwin.

In the End, One Great Beginning

There is much good news from all of the recent investigation of the epigenome. This companion coder of inheritance collaborates with DNA and impacts the health and well-being of current and future generations. Not long ago, the prevailing wisdom held that genes were the seat of destiny — not-so-great news for descendents of genetically defective parents and agony for the twin waiting to suffer the fate of his egg-mate. Hopefully, aberrations in epigenetic coding will prove easier to fix than "broken" genes; pharmaceutical companies are furiously searching for these biological switches, which, when flicked, could suppress genes for cancer, schizophrenia, autism and many other afflictions.

Lifestyle choices, including smoking and diet, can alter epigenetic marks and cause genes for obesity to be over-expressed and those for longevity to slumber silently. Scientists have new evidence that these choices have implications far beyond the individual. Says Pembrey: "Childcare [now] has a whole new meaning." "People," adds Jirtle, "have a responsibility for their epigenome. Their genome they inherit. But their epigenome, they potentially can alter, and particularly [the epigenome] of their children. And [this] brings responsibility, but it also brings hope."

By: Terri Sota

Sources:

- http://www.canada.com/ottawacitizen/news/observer/story.html?id=0e301579-a587-4825-961f-ee4eb4f690f9
- http://ghr.nlm.nih.gov/chromosome=1
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181727/
- http://www.time.com/time/magazine/article/0,9171,1952313,00.html
- http://sciencewatch.com/dr/erf/2008/08aprerf/08aprerfBayJones/
- http://www.ncbi.nlm.nih.gov/pubmed/18638373
- http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0030226
- http://www.sciencedaily.com/releases/2011/10/111020024333.htm
- http://www.futuremedicine.com/doi/full/10.2217/epi.10.40
- http://classic.the-scientist.com/news/20050707/02/