Looking Farther Afield

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Licking Pups into Shape

Evidence for the importance of epigenetic phenomena (e.g., imprinting and methylation of CpG islands) in development and in disease, is accumulating rapidly. Compelling evidence was derived recently from a study showing that the level of folate in the diet of a pregnant rat determined the degree to which the agouti trait was expressed in offspring—and the expression of the trait was fixed into adulthood.

Now, Weaver et al. (1) report that the extent of maternal grooming and licking of rat pups and arched-back nursing altered the methylation patterns at a glucocorticoid receptor in the pups and altered favorably their hypothalamic-pituitary-adrenal response to stress, and these changes persisted into adulthood. The effects were reversible by infusion of a histone deacetylase, which repressed the group differences in histone acetylation, DNA methylation, transcription factor binding, glucocorticoid receptor expression, and hypothalamic-pituitary-adrenal response to stress.

Conclusion: Maternal behavior alters the epigenome of the offspring, which in turn alters the behavior of the offspring. The nature-nurture relationship just became that much more complicated.—John D. Potter

MAPping the Causes of Crohn's Disease

There are some who argue that microbes will prove to be the causal agents of essentially all chronic diseases. Certainly, we have seen, over the last two decades, a high proportion of gastric pathology (chronic gastritis, peptic ulceration, and stomach cancer) laid at the door of a single bacterium. There is a growing body of evidence to implicate *Chlamydia* in heart disease, and it is now respectable, at least, to ask about a possible viral etiology of breast cancer.

It was just two decades ago also that saw the first report of the isolation of *Mycobacterium avium paratuberculosis* (MAP) from patients with Crohn's disease. The ''passenger or pathologic agent'' question, however, has meant that any causal interpretation remains controversial.

Naser et al. (2) took a new path, asking whether MAP could be detected in the blood of Crohn's patients at a greater frequency than normals. They found a higher proportion of Crohn's patients with MAP by PCR (46%) and culture (50%) than in controls (20% and 0%, respectively).

The data are not overwhelming but certainly add to evidence for a role of MAP in Crohn's and more widely for organisms in chronic disease, particularly where inflammation is central.

Koch's postulates cannot be invoked *in toto* for the relationship of infection with some chronic diseases. We need a new set of rules we can all live with. In their absence, we may go on missing treatable causes of chronic conditions, subjecting many thousands of patients to barbaric interventions (vagotomy, pyloroplasty, etc.) and death from bleeding or cancer—all for the want of an appropriate antimicrobial regimen. —John D. Potter

In a time when high school biology textbooks are being threatened with front-page stickers that read ''Evolution is just a theory,'' we need to keep the evolutionary banner flying high. Evolution matters at every level in biology—mass extinctions, ecologic change, origin of species, sexual selection, developmental biology all the way down to the way in which cancer cells undergo clonal expansion following (semi-)random mutation and selection by microenvironment, cell-cell interaction, and drug therapy.

So sometimes, the role of evolution will feature strongly in Looking Farther Afield. . .. Here are two interesting recent developments.

Circular Key

Phylogenetic trees allow the reconstruction of likely timing and sequence of divergence of species over evolutionary time. However, for unicellular organisms in particular, horizontal gene transfer (unicellular sex) and genome fusions (moving in and never letting go) make construction of the phylogenetic tree of early life extremely problematic.

The difference between prokaryotes (most unicellular organisms) and eukaryotes (all multicellular organisms, plus some unicellular) is profound. The eukaryote has a nucleus and organelles; prokaryotes have neither; their evolutionary relationship has been a matter of robust debate. Methods to establish that phylogenetic relationship have largely depended on ribosome gene sequences. The resulting trees, however, are not consistent with all the data, particularly the relationship between eukaryotes and archaebacteria.

Rivera and Lake (3) have analyzed hundreds of genes using a Markov-based method called conditioned reconstruction, rather than trying to build trees based on one gene. The method takes account of gene transfer between organisms. By not discriminating between vertically and horizontally transmitted genes, the method finds expected connections between prokaryote and eukaryote that are more complete than any single-gene method. It establishes the complex nature of the eukaryotic genome—related to both eubacteria and archaebacteria.

Rivera and Lake propose that this ring-like connection among prokaryote and eukaryote genomes arose because of the union between archaebacterial and eubacterial genomes, an endosymbiotic association between two prokaryotes. Thus, the process that saw the rise of eukaryotes was not divergence by usual Darwinian mechanisms but, as other data suggest, symbiotic fusion. One partner emerged from a photosynthetic clade (it is unclear which), the other is an archaebacterium.

The combination of mathematics, computation, and biology is a potent toolkit for solving ancient problems.—John D. Potter

Lousy Inferences about Human Origins

The origin of modern humans is a matter of considerable debate. There are two competing models, with variants. One model argues that *Homo sapiens* arose in Africa ~130,000 years ago and radiated from there, displacing the archaic *Homo* species in Asia, Africa, and Europe without interbreeding. A different model proposes that gene flow existed across *H. sapiens* and archaic humans (e.g., Neanderthals and *Homo erectus*) and that therefore there was some regional genetic continuity. Neither the primary models nor their variants are unequivocally supported by all the data. DNA from fossils to date have not been of sufficient range or quality to resolve the issues—and may never be so.

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Reed et al. (4) of the University of Utah sought answers using data beyond human genomics and archeology. Lice are host-species specific. The chimpanzee and the human louse diverged ~5.6 million years ago—consistent with the direct genetic evidence of the divergence of the two primate species. There are two human louse subspecies, which originally diverged 1.2 million years ago. One subspecies is distributed worldwide and infests both head and body. The other is exclusively a head louse and is found only in the Americas.

If there are divergent lice genomes, but now only one human species, the researchers reasoned that they may have diverged at the time of the split between Asian *H. erectus* and African *H. sapiens*. The extent of the divergence, and its inferred timing, suggests no gene flow between louse subspecies for ~1 million years. This suggests no contact between *Homo* species over the same period.

However, the fact that the louse subspecies, which is plausibly associated with *H. erectus*, made the jump back to *H. sapiens* argues for contact between *Homo* species—perhaps as recently as 30,000 years ago. It implies skin-to-skin contact and therefore sex or violence. Watch this space for data on pubic lice to help resolve the question.

So now, when people complain that the genetic data on human origins are lousy, it takes on a whole different meaning.—John D. Potter

References

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