The New Genetics

February 26, 2011

Frances Champagne

Back in the day, when you learned about genetics and evolution in school, it was all about Mendel and Darwin or more recent refinements of their basic ideas. As a bit of historical amusement, they also taught you about that other guy, Lamarck, who had oh-so-foolishly believed that traits acquired during an individual's lifetime could be passed on to offspring. They led you to think that silly notion was at the bottom of the dustbin of old, discredited science, right down there with the theory of bodily humors or an Earth-centered cosmos.

Who would have thunk it, that we are finally seeing the rehabilitation of poor old Lamarck in the new era of epigenetics? Who would have imagined that research uncovering the ability of life experience to alter the expression of genes would come along and, almost overnight, cause the old nature-versus-nurture debate — which practically defined psychology and the other social sciences for a century — to simply evaporate?

Who would have thought that DNA methylation could be so, well, interesting?

APS President Walter Mischel didn't try to contain his awe and excitement at this paradigm shift, when introducing the speakers at this year's Presidential Symposium. Three Canadians who are at the forefront of this new field, Frances Champagne, (Columbia University), Michael Meaney (McGill University), and Marla Sokolowski (University of Toronto), spoke about their respective discoveries concerning (as Mischel put it) "the gene by environment interactions that underlie what we become and how we differ."

What Makes Us Unique?

A vast and growing amount of data shows that life experience can shape an individual's development in amazingly subtle ways. Those influences can include nutrition and other environmental factors, as well as the amount of nurturance or stress experienced, especially early in life. The research of Champagne and her colleagues at Columbia shows that these influences involve actually facilitating or suppressing the expression of genetic information.

The metaphor Champagne uses is a library. A library contains many books, but they don't do anything by themselves; in order to have an impact, to instruct and inspire, they have to be actually taken down from the shelves and read. The genome is the same way: Whatever information it contains, it has no effect on anything unless and until it gets transcribed (by messenger RNA) and translated into protein. "DNA, in order to be read, must be accessible; it must be unwrapped from the very condensed form in which it is stored in cells," she explained.

Michael Meaney

Modifications such as the binding of methyl groups to the DNA (methylation) can affect how readily particular DNA sequences are read and, thereby, expressed. Changes in the cell environment influence methylation and, even more strikingly, these cellular changes are passed on to daughter cells. In other words, through epigenetic mechanisms — that is, functional changes in the genome that don't actually involve altering the DNA sequence — nurture plays an active role in shaping nature's expression, even from generation to generation.

In the case of Champagne's research, it's nurture literally: Specifically, how actively mouse mothers lick and groom their pups. Analogous maternal behaviors are common across mammals from mice to humans and are readily quantifiable in the lab. Champagne's research shows that, via methylation, high versus low levels of licking and grooming influence the expression of a gene that governs estrogen receptors in a key brain area responsible for maternal behavior. In this way, the amount of nurturance received by a mouse pup influences that pup's own maternal behavior later on — not merely as a matter of "learning," but as a real change in the expression of key genes in specific cells.

"Changes to the epigenome," she said, "are a cellular memory of an environmental event." Such cellular memories are then passed on to offspring via behavioral and epigenetic modes of transmission. In other words, Lamarck was right. Such acquired traits can also be undone if the environment changes again down the road. For example, the offspring of less nurturant moms, who would tend to be less responsive mothers themselves due to the effects described, can be put on a more nurturant track if they are placed in an enriched environment.

A Constant Dialogue

It is well known that the social environment in early life predicts the later health of organisms. The question is how. Champagne's mentor Michael Meaney discussed the hormonal mechanisms by which life experiences like early stress become, as he put it, "embedded."

"Development emerges as a constant dialogue between gene and environment," Meaney said, "and in part that environment is social and economic. â€¦ It is so for all species — it is social in that there is at least a maternal organism passing on signals to her offspring, and it is economic in that it involves at least nutrition, as well as potentially other signals." Such signals have a long-term impact on gene expression, through cellular mechanisms of methylation and other processes.

Meaney's work, like that of Champagne, looks at rodent maternal behavior — in this case, at its impact on later stress responsivity. The less licking and grooming infant rats receive, the more stress-reactive they are later. Offspring of more nurturant mothers are less easily stressed when they are adults than are offspring of less nurturant mothers. The same is true of offspring of less nurturant mothers raised by more nurturant foster mothers.

The hormonal mechanisms at work involve the body's stress homeostat, the hypothalamic-pituitary-adrenal axis. The stress response system begins in the hippocampus, which initiates a domino effect of chemical signals that ultimately trigger the release of glucocorticoid stress hormones by the adrenal glands. It’s a self-regulating system, in that these glucocorticoids ordinarily act back on the hippocampus, telling it to release fewer of its signals. In other words, stress hormones normally limit themselves.

But the stress of low maternal nurturance — less licking and grooming — early in life can directly influence the cell environment in hippocampal cells, producing increased methylation of the gene controlling for expression of glucocorticoid receptors and thereby inhibiting those receptors’ expression. The result is that the hippocampus is less responsive to signals to tone down the stress response — and consequently, there is heightened stress sensitivity and all the health and behavior consequences that entails. These influences (as in the alterations of maternal behavior studied by Champagne) can be passed on across generations but can also be reversed either pharmacologically or through alterations in the environment.

Following Meaney’s talk, Mischel voiced the unspoken question: “I wonder how many of you in the audience were thinking what I was thinking, which was ‘I wonder how much licking and grooming my mother did.'”

Rovers and Sitters

Marla Sokolowski

Fruit flies may seem nearly as remote from mice and rats as they are from humans, but the final speaker, University of Toronto biologist Marla Sokolowski, pointed out that many DNA sequences are now known to be present across organisms — “We can find a gene in the fruit fly, and we can say ‘Oh, this is the same gene in humans.'” Often, that gene will have similar functions in widely different species. The *foraging* (or *for*) gene found in most organisms is an example of this. It influences energy balance, food intake, and food-related movement and learning in flies, ants, nematode worms, bees, and even humans.

In fruit flies, the subject of Sokolowski’s work, the *for* gene influences how actively individuals forage for food (rovers) or sit tight (sitters) when they are near a known food source, as well as influencing the storage of fat and aspects of short and long-term memory. Yet the *for* gene shows plasticity of expression: How much of a key enzyme called PKG this gene makes — and thus, how it expresses itself — depends on the environment. After chronic deprivation of food — equivalent to “a low-SES [socioeconomic status] background for fruit flies” — rovers, who ordinarily take in and store less food than sitters, behave more like their more sedentary counterparts.

Sokolowski explained that, in a range of other animals such as ants and honeybees, the expression of *for* similarly varies based on environmental as well as behavioral factors, pointing to a strong interdependence between genetics and the environment across species.

Fruit flies may even provide a model for the role of the *for* gene in humans. Sitter flies are better at responding to seasonal signals than rovers, Sokolowski said — when days get short, sitters go into a kind of hibernation. This overwintering resembles seasonal affective disorder (SAD) in humans: During the winter months, SAD sufferers increase their food intake and decrease their activity. And indeed, a study of people with severe SAD and a control group revealed an association between the disorder and their *for* genotype.

Mischel summed up the symposium presentations by reiterating what an exciting time it is for psychology, as this “new genetics” lead us away from the dichotomous thinking that so long divided the field into antagonistic subdisciplines. The presentations highlighted, he said, “the foolishness and the narrowness of remaining within little subdisciplines and asking each other questions like ‘Are you a personality psychologist or a social psychologist or just what are you?'”

“We see,” he said, “a complete crossing of boundaries, where one doesn’t know what the hell one is, but it certainly is interesting.”