Invited Commentary

Embracing the chaos of behavioral proteomics: a comment on Valcu and Kempenaers

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It is tempting to feel nihilistic when an avalanche of anonymous omic data is bearing down on you. Particularly if you are studying a trait as variable, flexible, nuanced, and generally misbehaved as behavior. And even more so if you are trying to do it in a non-model organism. Nevertheless, Valcu and Kempenaers (2014) argue that behavioral ecologists should take advantage of recent technical advances to apply high-throughput proteomics to behavioral research, much the same way transcriptome profiling now features in many behavioral studies, and they highlight a range of studies that have identified proteins underlying interesting behavioral phenotypes such as sexual conflict and communication. Such progress is encouraging, but we would like to highlight an additional exciting prospect of a behavioral proteomics research program.

We advocate a complementary conceptual approach that takes advantage of the immense complexity and sensitivity of the proteome. High-throughput proteomics is a valuable tool for generating hypotheses about candidate proteins, but as Valcu and Kempenaers (2014) point out, a considerable effort is then required to establish a causal link between protein variation and corresponding behavioral variation, much less the direction of that link. The technical expertise required to reach such a point is likely a much larger hurdle to behavioral ecologists studying nonmodel organisms than is the quantitation of peptides in a mass spectrometry (MS) screen. As an alternative to focused single-protein investigations, it may be useful to directly work with whole-proteome signatures to test hypotheses about the molecular mechanisms and evolutionary origins of interesting behaviors. The unit of study would be the proteome itself, not a protein. This framework is particularly apt for behavioral ecologists; the dynamic range of protein expression can be an order of magnitude greater than that of mRNA expression, proteomes can vary temporally and spatially, and a staggering array of post-translational modifications such as phosphorylation, selective degradation, and differential folding make them exquisitely responsive to environmental perturbation (Ahmad and Lamond 2014).

The chaotic nature of the proteome is one of its most intriguing features, and perhaps the clearest impact of this chaos can be illustrated by considering the proteomic basis of phenotypic plasticity. Understanding how behaviors respond to delicate variations in social or ecological contexts can be enhanced by identifying and categorizing how such environmental noise disturbs the genotype-to-phenotype map. Valcu and Kempenaers (2014) illustrate key studies that describe proteins whose expression correlates with phenotypic plasticity, but these are largely restricted to understanding caste determination in eusocial insects, and they tend to focus on behavioral traits that co-occur with other morphological and developmental changes that may not be readily reversible. In contrast, behaviors such as parental care or differential aggressive responses depending on the social environment (Smiseth and Moore 2002, Logue et al. 2010) are much more dynamic and reversible. Testing proteome-wide patterns associated with such behaviors implicitly acknowledges their complex polygenic basis and environmental sensitivity.

There is precedent for testing hypotheses about whole-proteome variation, and ingenious methods for doing so (Ohta et al. 2010, Khan et al. 2013). Recent work has refined analytical techniques for assessing and testing broad patterns of variation across proteome profiles. For instance, Ly et al. (2014) used global transcriptomics and proteomics analysis to determine the pattern of expression of mRNAs and their cognate proteins across the cell division cycle, and similar approaches could be taken to identify co-ordinated versus discordant mRNA and protein expression levels associated with behavioral phenotypes of interest. Such information would not only clarify the molecular bases of variation in behavior, but could ultimately provide a foundation for testing how selection acting on behavioral variation is—or is not—converted into allele frequency changes. It is important to emphasize the need for explicit hypothesis-testing; for instance, one might test whether less dynamic proteomic components of a phenotype are more resistant to selection, thus channeling evolutionary responses toward more environmentally sensitive proteomic pathways. This could address a longstanding question about the evolution of behavior, which is the relative importance of behavioral flexibility in setting the pace for evolutionary change (West-Eberhard 1989).

We certainly would not argue against candidate gene/protein approaches in behavioral ecology. However, if ever there was a capricious trait likely to be influenced by miniscule, fleeting variations in the expression of a large number of proteins, it is behavior. An additional advantage of a systems approach is that testing hypotheses about behavioral proteomics need not rely on highly detailed gene annotations (Wuhr et al. 2014). For example, experimental evolution studies such as are performed in Drosophila lines subjected to varying opportunity for sexual selection could assess whether more socially responsive constituents of the genotype-to-phenotype map show correspondingly slower or faster responses to selection, without needing to know the function of the genes involved (Immonen et al. 2014). These genotype-to-phenotype maps are already being used to enrich the annotation of the human genome by associating molecular signatures to both simple and complex phenotypes, such as gene
deletion and disease (Subramanian et al. 2005). In the immediate future, we anticipate the “cleverest” experiments will use the avalanches of anonymous “omic data currently being generated to deliver insights into the evolutionary and molecular constraints—and evolutionary and molecular paths-of-least-resistance—that cause interesting behavioural variation in nature. Embrace the chaos of the proteome!

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