Cross-bred flies reveal new clues about how proteins are regulated

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Proteins are the go-getters of a cell. They carry out all the jobs that are required for cells to grow, reproduce and perform other duties. But genes carry instructions for far more proteins than are present in a cell at

any one time. Therefore, it's useful for researchers to know the set of proteins present, or the proteome, in a cell or tissue at a given time and under certain conditions. Understanding the size limits of a proteome and a cell's tolerance for protein diversity is critical for determining how organisms evolve.

Now, a team from The Scripps Research Institute (TSRI) has revealed that by crossing two species of flies, they can use what they learn from the proteome of the hybrid offspring to find new clues about how proteins interact with each other—and under which circumstances additional proteins are tolerated. They reported their findings recently in the journal *Science Advances*.

"We were surprised to find that during embryonic development, the proteome of the hybrid offspring has more complexity and more proteins than what would be found in both parent species combined," says Casimir Bamberger, PhD, a TSRI research associate and the study's first author. "It showed us that the proteome harbors a plasticity during development that is later lost in adulthood. This increased plasticity of the proteome during development might provide additional space for rapid phenotypic variation when organisms evolve."

The investigators used a technique called bottom-up proteomics (sometimes called shotgun proteomics) to reveal which proteins of each species were present in the hybrid flies. In this process, proteins are digested into smaller peptides, and those peptides are analyzed with mass spectrometry (MS), which measures masses of molecules within a sample. Because masses differ between peptides from either species, researchers were able to trace back the proportion of proteins that each species' genome contributed to the proteome in hybrids.

"MS is the only large-scale method to study whole proteomes," says John Yates III, PhD, a professor in TSRI's Department of Chemical

Physiology and the study's senior author.

His lab is focused on the development and application of MS-based proteomics techniques to answer a wide range of biological questions. "We can use this technology to both identify and quantify thousands of proteins in a sample at the same time," he adds.

In the study, the researchers cross-bred two species of fruit flies, *Drosophila melanogaster* and *Drosophila simulans*. Fruit flies are popular models for studying genes and proteins because they are well understood and relatively easy to manipulate in the lab. The proteins from the hybrids and the two parents were labeled with different isotopes so the scientists could determine which proteins in the offspring differed in its amount from the parent.

The investigators found that during early development, the flies expressed new proteins not detected in either of the parental species during the same point in their development. However, the number of proteins was reduced in the surviving adults. This provided researchers with new details about the function of the proteostasis network—a regulatory system within cells that coordinates how proteins are synthesized, folded, modified and degraded, among other roles.

"We found that in these developing hybrids, the increase in proteome complexity was accompanied by an upregulation of the proteostasis network, which means it was more active than usual," Bamberger explains. "This is because it's busy removing proteins that it recognizes as not being in place. But on the other hand, the proteostasis network might also be contributing to how new and additional proteins are stabilized and thereby sustained within the organism."

Bamberger says that by studying the proteostasis network and how proteins interact with each other, the team can begin to understand why

certain proteins are maintained in the proteome despite their malfunction, for example, in conditions like cancer or neurodegenerative disorders including Alzheimer's disease. Understanding these interactions could one day lead to novel approaches for treating some diseases.

"Gaining more insight into the fundamental principles that govern protein-protein interactions on a large scale might help us understand how species accomplish rapid phenotypic variation or how diseased cells keep a proteome up and running with increasingly mutated proteins," Bamberger explains.

Yates added that the study was also a useful tool for understanding animal breeding. "It shows us how much genetic change prevents species from successfully mating and what is happening at the protein level when that does occur," he says.

More information: Casimir Bamberger et al, Increased proteomic complexity in Drosophila hybrids during development, *Science Advances* (2018). DOI: 10.1126/sciadv.aao3424

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