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How Dad's Stresses Get Passed Along to Offspring

Mouse studies show tiny intercellular pods convey to sperm a legacy of a father's hard knocks in life

By Esther Landhuis on November 8, 2018

A stressed-out and traumatized father can leave scars in his children. New research suggests this happens because sperm "learn" paternal experiences via a mysterious mode of intercellular communication in which small blebs break off one cell and fuse with another.

Carrying proteins, lipids and nucleic acids, these particles ejected from a cell act like a postal system that extends to all parts of the body, releasing little packages known as extracellular vesicles. Their contents seem carefully chosen. "The cargo inside the vesicle determines not just where it came from but where it's going and what it's doing when it gets there," says Tracy Bale, a neurobiologist at the University of Maryland School of Medicine.

Preliminary research Bale and others, announced this week at the annual meeting of the Society for Neuroscience in San Diego, shows how extracellular vesicles can regulate brain circuits and help diagnose neurodegenerative diseases—in addition to altering sperm to disrupt the brain health of resulting offspring.

Striking evidence that harsh conditions affect a man's children came from crop failures and war ravaging Europe more than a century ago. In those unplanned human experiments, prolonged famine appeared to set off a host of health changes in future generations, including higher cholesterol levels and increased rates of obesity and diabetes. To probe the inheritance of such changes at the cellular level, Bale and co-workers performed a series of mouse experiments.

It is pretty easy to stress out a mouse. Stick one into a tube it cannot wriggle out of, soak its bedding or blast white noise—and stress hormone levels shoot up, much as they do in people worrying about finances or facing incessant pressure at work. Remarkably, the way a mouse physiologically responds to stress looks noticeably different if—months before conception—its father endured a period of stress. Somehow "their brain develops differently than if their dad hadn't experienced that stress," says Chris Morgan, a postdoc in Bale's lab who helped create the mouse model.

The big question is how information about the paternal environment reaches the womb in the first place. After all, Morgan says, the "dad is only in there for one night, perhaps just a few hours." Could his sperm carry memories of prior trauma? The idea seemed reasonable yet controversial. Because DNA is packed so tightly in the nucleus of a sperm cell, "the thought that [the cell] would respond to anything in the environment really boggled people's minds," says Jennifer Chan, a former PhD student in Bale's lab who's now a postdoc at Icahn School of Medicine at Mount Sinai in New York City.

Rather, there must be some other kind of cell whose DNA does react to environmental changes—and that cell, she reasoned, could then relay that information to sperm cells to transmit at fertilization. She focused on a population of cells that interact with developing sperm by releasing molecules that help sperm grow and mature. They also secrete extracellular vesicles—and Chan showed it is these vesicles whose contents fuse with sperm cells, instilling memories of dad's prior stress.

In one set of experiments Chan stressed a group of male mice, let them mate and looked at stress responses in the pups. The clincher was a set of in vitro fertilization–like experiments in which she collected sperm from a male mouse that had never experienced induced stress. Half his sperm went into a lab dish with vesicles previously exposed to stress hormones. The other half was cultured with vesicles that had no contact with stress hormones.

Chan injected sperm cells from each batch into eggs from a nonstressed female, then implanted the fertilized eggs—zygotes—into the same foster mom. The pups from nonstressed zygotes developed normally. Pups from stress-exposed zygotes, however, showed the same abnormal stress response as those whose dads had experienced stress before mating. That showed extracellular vesicles act as the conduit for transmitting paternal stress signals to the offspring, Chan says.

The findings are "novel and of very high impact, especially when we consider the impact of military service or other work environments that can confer high stress," says Robert Rissman, a neuroscientist at the University of California, San Diego, who was not involved with the research. "I think it would be important to better understand the specificity of the effect and how different types of stressors or strength of stressors can modulate this system."

As a first step toward translating the findings to people, Morgan is collaborating with University of Pennsylvania psychiatrist Neill Epperson to track protein and RNA changes in human sperm samples. At the neuroscience meeting, Morgan presented data from a six-month study of 20 undergraduate and graduate students. Each month the participants came in and gave a sperm donation. They also completed a same-day survey asking how stressed they were feeling. Preliminary data suggests just several months after a student reports stress, his sperm shows changes in "small noncoding RNAs"—RNA molecules that do not get translated to protein but instead control which genes get turned on or off.

Analyzing sperm from this group of healthy young men, the researchers plan to build a basic understanding of molecular changes linked with mild stresses such as taking final exams. In the future Bale and colleagues hope to compare these baseline fluctuations with changes induced by more prolonged life stressors such as post-traumatic stress disorder or neurological diseases such as autism and schizophrenia.

The molecular signatures in extracellular vesicles may also help researchers discover new ways to noninvasively diagnose or predict adverse health outcomes in offspring, says Gerlinde Metz, who studies transgenerational inheritance of stress responses at the University of Lethbridge in Alberta and was not involved with the research. If so, the vesicles could become the basis for a pioneering type of stress test.

AABE Hackathon

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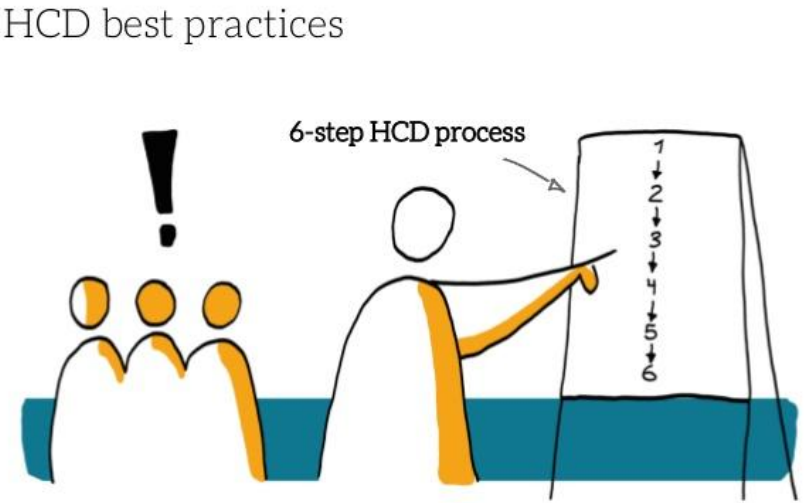
6 steps in Human Centered Design Process

- Identify
- Immerse
- Reframe
- Ideate
- Build
- Test



Identify

Goal: Defining the targeted problem space you will tackle.

Outputs: 4-5 broad questions that define the problem spaces to research.

Key Questions:

- What are the facts, assumptions, and problem space you can identify about the larger problem?
- What local organizations and mentors can you work with to help tackle this challenge?
- What are 2-3 initial How Can We's that will help focus research in your problem spaces?

Immerse

Goal: Empathize with end-users (stakeholders) and uncover insights to deeply understand your problem spaces.

Outputs: Empathetic stories of stakeholders. 2-3 key insights along with visual representation.

Key Questions:

- What are interesting facts, stories, themes and existing solutions from your secondary research that you are excited to explore further?
- Who are stakeholders within your problem spaces? Organizations? Places?
- What are 2-3 key insights along with visuals to explain those insights?

Reframe

Goal: Define the change you want to make in the world and what your solutions needs to accomplish to get there.

Outputs: 3-4 Design Goals defining desired solutions qualities.

Key Questions:

- Based off of your teams research and insights, what qualities does your solution need for it to be effective? (These are your Design Goals)
- What end results will indicate that future solutions impact your users' lives? (These are your measures of success)

Ideate

Goal: Generate a variety of ways that make change and explore many alternative solutions.

Outputs: List of 10+ different ideas. 2-4 well-considered concepts..

Key Questions:

- What are some of your wildest ideas? Safest ideas? Easy to implement ideas? Difficult to implement ideas?
- What are themes or categories that your different ideas begin to explore?
- Based on alignment with your design goals and measures of success, what 2-4 concepts are you going to build?

Build

Goal: Make a variety of tangible prototypes to communicate your ideas.

Outputs: At least 2 built prototypes of every concept you're moving forward with for user testing and feedback. A list of important questions to learn about each concept..

Key Questions:

- What are at least 2 different ways you are prototyping each concept?
- What are the simplest ways that you can prototype your concepts to quickly get user feedback?
- What are the important questions you have about each of your concepts that you need to learn as you build your prototypes?

Test

Goal: Get feedback to uncover insights and develop next steps to improve a solution.

Outputs: 4-5 user/expert quotes about your solution. 2-3 insights to inform next steps.

Key Questions:

- How are you ensuring that your tests will help you answer the important questions you have for each concept?
- What quotes and stories from users and experts stood out to you during testing?
- What insights from testing are directing further research and ideation?