How the effects of trauma can be inherited through epigenetic mechanisms

March 14 2023, by Fabio Bergamin

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Our parents and grandparents form part of who we are. They reared us and served as our role models, and they also passed on their genes. That's why we are similar to them, and why we share a genetic predisposition to develop certain diseases. Yet genes may not be the only molecular factors we inherited from them. The effects of the lifestyle and experiences of previous generations—including how well they ate and whether they suffered emotional trauma—can also be passed down through the generations via biochemical markers in sperm and egg cells.

A study conducted in the village of Överkalix in northern Sweden, which analyzed family data stretching back over more than a century, showed that the sons of men who ate a hearty diet as children had a higher risk of cardiovascular diseases than the sons of men who grew up on leaner fare. The effects of diet even extended to the second generation: the grandsons of men who ate abundantly had an elevated risk of diabetes.

We also know that traumatic conditions in early life, physical or sexual abuse and violence affect health across generations. These increase the risk of depression, anxiety, personality disorders and metabolic and cardiovascular diseases. The children of Vietnam War veterans and Holocaust survivors are more likely to suffer from post-traumatic stress disorder and depression. Scientists as well as psychologists, psychiatrists and social workers have long been aware of such intergenerational effects, but are not clear on what causes them. Professors Isabelle Mansuy and Katharina Gapp have been working on this question—and their findings suggest that so-called epigenetic factors play a role.

Epigenetic factors are an ensemble of molecules or molecular tags on and around the DNA that do not directly change its sequence (the genetic code). Instead, they regulate DNA activity and the expression of genes by complex molecular and structural processes.

Like DNA, which is transmitted from parents to children, epigenetic factors in germ cells can also be inherited. It is not known, however, if these factors are inherited in full, and if they are modified by a traumatic experience or poor diet, how many downstream may be affected. Today, symptoms are known to be passed down from one generation to the next, but more research is needed to determine if epigenetic anomalies persist across generations.

This is particularly relevant with respect to stress and trauma experienced by victims of child abuse or domestic violence and by refugees fleeing conflict. The psychological scars inflicted on trauma survivors are already tragic enough. But if the effects extend to their descendants, this makes the number of victims considerably higher.

Characteristic signature

Mansuy and Gapp studied how the effects of trauma are inherited in mice. They were able to show that male mouse pups that are exposed to stress over long periods of time grow up to become antisocial adults that display depression-like symptoms, greater risk-taking behavior and memory deficits. When the researchers mated these animals with control mice and studied their offspring, they discovered that the next generation also exhibited the same kind of altered behavioral patterns, with some of the abnormal behaviors even persisting into the fifth generation.

Gapp began her research career several years ago as a doctoral student in Mansuy's group. Today, she runs her own research group at ETH Zurich. During her doctoral project, she discovered that the RNA profile in sperm is partly responsible for passing on the effects of stress in mice. To demonstrate this, she analyzed thousands of RNA molecules from sperm cells of animals that had been exposed to traumatic stress themselves, or whose fathers had experienced stress, and compared them with those of non-traumatized control group animals.

In this way, she was able to identify a characteristic signature of these

RNA molecules that was only found in traumatized animals. In a subsequent experiment, she isolated RNA from the sperm of traumatized male mice and injected it into fertilized eggs produced by non-traumatized parents. The results confirmed that sperm RNA was passing on information about prior trauma—a clear case of epigenetic transmission.

Unpredictable stress

Gapp's work built on a pioneering model developed by Isabelle Mansuy that helps researchers study the effects of stress and emotional trauma in mice. In Mansuy's model, pups are separated from their mother for three-hour stretches at random, unpredictable times. This is repeated every day over a two-week period. In addition, the mothers are subjected to severe and unpredictable stress situations.

The fact that RNA may be an indicator of past traumatic experiences not only in mice, but also in humans, was demonstrated by another doctoral student in Mansuy's group. The researcher carried out a study in collaboration with SOS Children's Villages Pakistan and a Pakistani biological diagnostic laboratory. In one of the studies, he was able to show that the quantity of certain RNA molecules in the blood of orphaned children was different from that of the control children. The same RNA molecules were also altered in the blood of adult men raised as orphans. In a more recent study, which has already been peer-reviewed but not yet published, he was also able to show that men who experienced one or more traumatic events in their childhood exhibit changes in their sperm RNA molecules.

However, RNA is probably not the only molecular factor through which the effects of trauma are inherited. The way in which chromosomes are spatially organized in sperm—in other words, whether they are closely packed together or more loosely arranged at certain points within the cell nucleus—may also be significant. Numerous proteins are able to bind to DNA in a way that affects chromosome structure. And it is this structure that has an influence on which genes are active or not in the cells during processes such as embryonic development.

One of the proteins that binds to chromosomes is the glucocorticoid receptor, which interacts with the hormones released in response to stress as well as with the hormonally active agents that can be found in solvents, plastic products and pesticides. Gapp therefore suspects that combined effects may occur when, for example, someone who is already exposed to pollutants and eats an unhealthy diet also experiences trauma.

"As the evidence mounts that men's behavior prior to conception may play a role in the embryonic development of their offspring, we're starting to see men sharing responsibility for the health of their unborn children," says Gapp. Until now, this burden has been placed squarely on the shoulders of the expectant mother in the form of advice such as abstaining from alcohol and giving up smoking during pregnancy.

Positive news

Yet even if the epigenetic effects of trauma have so far primarily been found in fathers and their descendants, this does not exclude the possibility of intergenerational effects involving female germ cells, called oocytes. Put simply, researchers have studied inheritance via the female germline far less because it is much harder to obtain oocytes, which are rare, than sperm cells.

Even though the epigenetic effects of traumatic events may echo through generations, the good news is that they are reversible. Gapp demonstrated this in mice by exposing traumatized pups to environmental enrichment. As well as being placed in larger groups and given bigger enclosures, the mice had access to objects that encouraged them to move and explore. As a result, many of the symptoms that traumatized mice would otherwise exhibit, such as increased risk-taking behavior, disappeared. The stimulating environment reversed the effects of trauma not only in the previously traumatized mice, but also in their subsequent offspring. In a smaller study, the researchers confirmed this reversibility not only in the animals' behavior, but also on a molecular level in individual epigenetic factors. "The main characteristic of epigenetic changes is that, unlike genetic changes, they can be reversed," says Mansuy.

This ties in neatly with our knowledge of psychology and psychiatry. The earlier an abused or otherwise traumatized child begins therapy, the greater the chance of minimizing any long-term effects. Mansuy's and Gapp's research is helping to change our perception of mental health. "Unfortunately, people with mental health disorders are sometimes made to feel that they have brought their situation upon themselves," says Mansuy. But if hereditary factors play a role in the development of such disorders, such presumptions become even less plausible than before.

Provided by ETH Zurich

Citation: How the effects of trauma can be inherited through epigenetic mechanisms (2023, March 14) retrieved 26 April 2024 from https://medicalxpress.com/news/2023-03-effects-trauma-inherited-epigenetic-mechanisms.html