Molecular effects of traumatic stress

After a traumatic experience, people often suffer not only mental, but also physical effects. Dr. María Moreno-Villanueva from the University of Konstanz has investigated the molecular effects of traumatic stress in people and has found a higher than normal number of DNA strand breaks. In the worst cases this can lead to diseases such as cancer. However, her study also shows that successful psychotherapy can reverse DNA damage. Her findings will contribute to the development of new methods for the diagnosis and therapy of traumatic stress disorders.

Traumatic experiences such as a serious accident, natural disasters or war may have serious consequences for the people concerned. These consequences might reach far beyond the actual event. People who are still experiencing severe psychological disorders many years after being exposed to a traumatic event are said to suffer from a disorder known as posttraumatic stress disorder (PTSD). Symptoms can include psychological conditions such as depression, personality changes or disturbed memory. However, the disease can also have physical effects: in addition to an increased risk of cardiovascular or autoimmune diseases, PTSD is also associated with increased mortality. However, the molecular mechanisms underlying these symptoms are not yet understood in detail.

“PTSD has been associated with changes in immune system modulators, DNA methylation patterns and transcription factors. However, the exact relationships are unclear,” says Dr. María Moreno-Villanueva, a scientist in the Department of Molecular Toxicology at the University of Konstanz. Her research is specifically focused on studying the repair mechanisms of DNA damage and biomarkers of human ageing, but also on DNA modifications in the mentally ill. She is taking part in an interdisciplinary project in which she has been investigating the molecular effects of posttraumatic stress in patients.

When stress makes us older

Dr. María Moreno-Villanueva investigates molecular ageing processes and DNA alterations caused by traumatic stress.

Dr. María Moreno-Villanueva developed the idea for the project together with psychologist Prof. Dr. Iris-Tatjana Kolassa, who, up until 2010, was the head of the independent Emmy Noether Junior Research Group "Stress and trauma-associated immunological changes and their health implications" funded by the German Research Foundation. As patients suffering from posttraumatic stress disorders often display signs of accelerated ageing, the researchers, as a natural consequence, decided to look for molecular biomarkers of ageing.

Kolassa therefore contacted a group of researchers in the Department of Molecular Toxicology led by Professor Alexander Bürkle where Dr. Moreno-Villanueva was working. "Back then, the most suitable biomarkers to indicate a person's biological age were still unknown," says Moreno-Villanueva. However, it was known from previous scientific studies that DNA damage accumulates with age and Moreno-Villanueva suggested studying the occurrence of DNA strand breaks in those affected.

"I was extremely interested in finding out whether traumatic stress compromises DNA integrity," says Moreno-Villanueva. The researchers involved in the cooperative project took blood samples from patients and control subjects, and isolated cells known as peripheral mononuclear blood cells (PBMCs). In patients suffering from posttraumatic stress disorder, samples were taken before and after successful psychotherapy. The DNA strand breaks were subsequently determined using an assay known as "fluorescence-detected alkaline DNA unwinding" (FADU) (see article entitled "Technical innovations for better diagnostics"), which was optimised and automated by Bürkle and Moreno-Villanueva and enables the reliable, quantitative determination of DNA strand breaks in blood samples.

Measurable therapy success on the molecular level

The researchers analysed samples from 60 people and found distinctive differences between the sick and the healthy. In general, chronically traumatised patients had a much larger number of DNA strand breaks," says Moreno-Villanueva. The accumulation of non-repaired DNA strand breaks can disrupt important cellular functions and even lead to cell death. It can also lead to mutations, i.e. permanent changes in the genome. "If DNA sections that regulate cell division are affected, the breakage can also lead to cancer," says Moreno-Villanueva.

The researchers' study also suggests that there are ways to prevent such serious consequences. They were the first to show that patients who had undergone successful psychotherapy did not have a significantly higher number of DNA breaks than the healthy volunteers. This molecular evidence for the effectiveness of psychotherapy is a scientific novelty.

In order to provide further evidence for the assumed acceleration of the ageing process, Moreno-Villanueva also investigated another marker in the patients' blood. "The concentration of specific sugar molecule chains, so-called N glycans, in the blood plasma changes with age. This is why we have also studied the N glycan profiles of the PTSD patients," says Moreno-Villanueva.

The results of the study clearly evidenced what the subjective self-assessment of the patients suggested. "We have shown that chronically traumatised patients have an N glycan profile which corresponds to that of a healthy person 15 years older than the patient," she explains.

DNA strand breaks were investigated using the automated FADU assay, which was optimised by María Moreno-Villanueva during her doctoral work in Professor Alexander Bürkle's laboratory at the University of Konstanz.

From patient back to research lab

The finding that DNA damage can be caused by traumatic stress leads to new hypotheses and research projects. Other scientists have shown for example that the chronic stimulation of cells with adrenalin leads to a reduction in p53 expression. p53 is a key DNA repair regulation and cell cycle enzyme. The reduced expression of p53 weakens the cellular defence system, resulting in increased DNA breakage.

"However, adrenalin is probably not the only factor that has such an effect," says Moreno-Villanueva. In order to obtain further insights into the underlying mechanisms, she is now examining the relevant cellular signalling pathways in an ex vivo model. To do this, she is using freshly isolated immune cells from healthy young volunteers. The immune cells are then grown in cell cultures. "We know how DNA damage occurs. Reactive oxygen species can induce DNA damage for example. One might therefore speculate that chronic stress leads to an increased production of reactive oxygen species and hence to DNA strand breaks," explains Moreno-Villanueva.

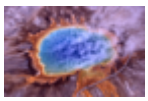
Further information:
Dr. María Moreno-Villanueva
Department of Molecular Toxicology
University of Konstanz

E-mail: maria.moreno-villanueva(at)uni-konstanz.de

Article

08-Sep-2014
Bettina Baumann
BioLAGO

The article is part of the following dossiers



Stress and molecular defence mechanisms