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A strange combination: green tea extract and light for treating Alzheimer's

Andrei Sommer from the University of Ulm and colleagues from Ulm, Heidelberg and Berlin have succeeded in reducing amyloid beta deposits in human neuroblastoma cells by up to 60 per cent in vitro. The researchers found that the apparently strange combination of green tea and red light has the potential to lead to the development of new therapies for Alzheimer's. There are currently no treatments available that stop or reverse the progression of the disease.

The cause(s) of Alzheimer's are not well understood. Research indicates that Alzheimer's disease is associated with protein deposits in the brain, i.e. extracellular plaques consisting of amyloid beta peptides and intracellular tau fibrils. However, it is not yet known whether the deposits – either together or singly – cause Alzheimer's or are merely epiphenomena that occur as the disease progresses. Researchers have for quite some time been discussing the controversial prion theory, linking the underlying mechanism of prion diseases with that of Alzheimer's disease (e.g. Kim/Holtzman, Prion-Like Behavior of Amyloid-β, Science, 12.11.2010, DOI: 10.1126/science.1198314). Only recently, two series of animal experiments have provided evidence of the infection-like spread of the tau protein from one cell to another and have caused a sensation (Kolata, NYT).

Amyloid beta peptides are fragments of the membrane protein (amyloid precursor protein) produced by neurons. In healthy brains, these fragments are degraded and destroyed. In brains of people suffering from Alzheimer's disease, however, these fragments accumulate and form insoluble extracellular plaques. Intracellular amyloid beta plaques are also toxic. The smaller soluble fragments (oligomers) have been shown to have the strongest toxic effect of all fragments investigated. The neurotoxic mechanisms are not yet well understood, but mutations in the genes that are responsible for the production and metabolism of amyloid beta have been identified in early-onset Alzheimer's disease.

The trouble with tau

Tau fibrils are insoluble, twisted neurofibrillary protein tangles found inside neurons. The pathophysiological aggregation of tau proteins represents an own class of neurodegenerative diseases, which are known as tauopathies. In healthy brains, the tau (tubulin-associated unit) protein stabilizes the tubular filaments (microtubuli; around 25 nanometres thick) of the neuronal cytoskeleton. The microtubuli play an important role in the transport of nutrients and other vital substances inside the neurons. In the brains of Alzheimer's sufferers, the tau protein loses its

stabilizing function, tau tangles are formed and the microtubuli disintegrate, thereby leading to the death of neurons.

Nanoscientist Dr. Andrei Sommer.
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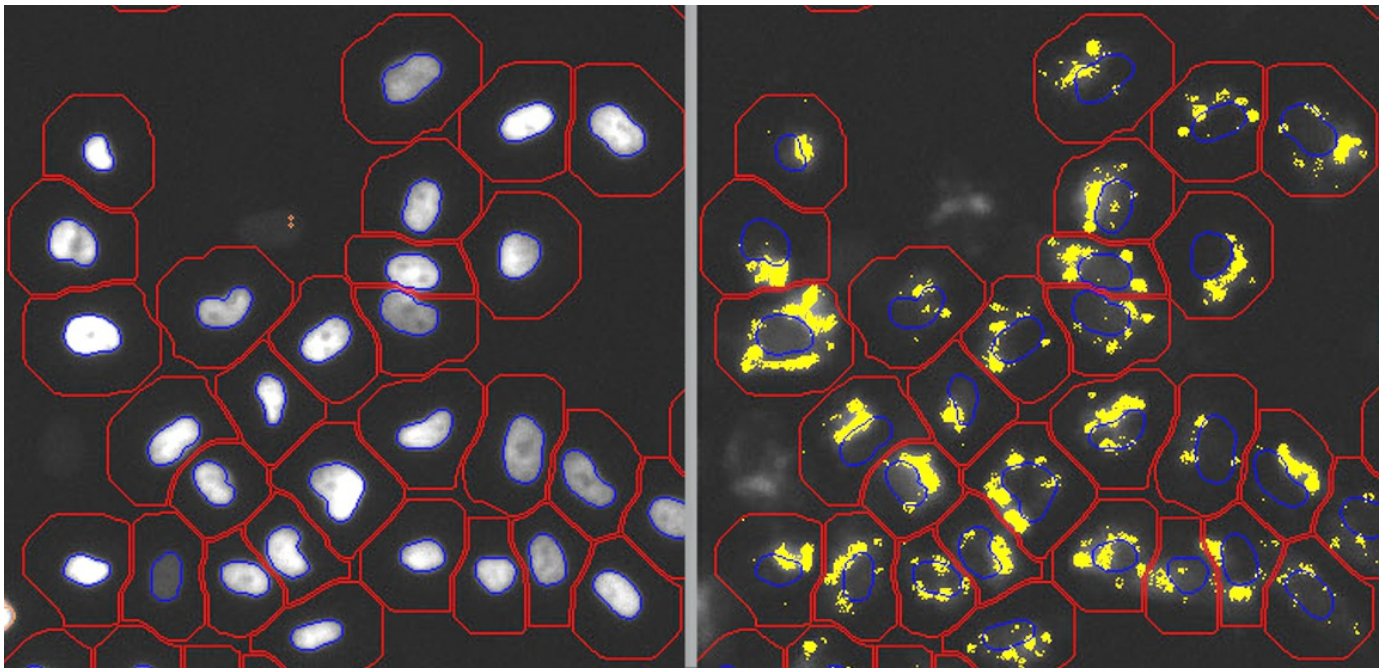
In the study, which was recently published in the scientific journal “Photomedicine and Laser Surgery”, human neuroblastoma cells that had taken up amyloid beta 42 (Ab42) were treated with two components: laser light with a wavelength of 670 nanometres and/or green tea polyphenol by the name of epigallocatechin gallate (ECGC). The experiments were carried out at the Max Delbrück Centre for Molecular Medicine (MDZ) in Berlin.A group of MDZ researchers led by Erich Wanker is focusing on the investigation of the molecular mechanisms of neurodegenerative diseases. According to Sommer, Wanker’s group is a worldwide leader in the

investigation of the interaction of EGCG and amyloid beta. In 2010, the MDZ researchers showed in vitro that the green tea EGCG converts amyloid beta deposits into nontoxic compounds (Bieschke, 2012; Ehrnhöfer, 2008).

Combination proved to be most effective

“We bathed brain cells containing amyloid beta in ECGC and found that amyloid beta in the neuroblastoma cells reduced by around 50%. Irradiating the cells with laser light alone reduced amyloid beta by around 20 per cent. When we used EGCG at the same time as stimulating the cells with red light amyloid beta aggregates were reduced by more than 60 per cent,” said Sommer summarizing their results which have since been the subject of fervent discussion. Laser light with a wavelength range in the red to near-infrared range and similar intensity has been used in clinical wound treatment for more than 40 years.

In the USA, transcranial penetration of red to near-infrared light is used for the treatment of patients with acute stroke and with acute and chronic traumatic damage, Sommer explains. It is not yet known whether the success achieved in the treatment of chronic traumatic brain damage that occurs in some sports (e.g. boxing, American football) might be associated with progressive tauopathies (Miller, 2009).



Human neuroblastoma cells are an established cell model. Left (cell nuclei (blue) and cell membrane (red contour), right: fluorescence-labelled Aβ deposits (yellow).

Does this approach also have an effect on tau protein?

The application of this rather unusual combination of laser light and green tea extract is subject to further research; initial evidence for the effect of the combination has already been found. “We are only just beginning,” said Sommer who believes that research into the application of laser light, green tea extract and other plaque destroyers is highly promising. “We are currently developing approaches involving laser light, green tea extract and other agents, which we hope to be able to use to destroy amyloid beta oligomers,” said Sommer without disclosing further details of their research.

For non-scientists, the nanoscientist’s experiments might appear to be a rather unusual foray into

the field of biomedicine. However, for Andrei Sommer from the Institute of Micro- and Nanomaterials at the University of Ulm it was a case of "the systematic application of simple biological models". The models are based on state-of-the-art basic research-oriented (experimental and theoretical) work into nanoscopically thin water films on nanocrystalline diamond substrates. Sommer explains that the models and the necessary measurement technology were available at the institute and "were the key for all our work."

Light pushes water out of the cells

The nanoscientists and engineers from Ulm carried out investigations of nanoscopically thin water layers on nanocrystalline diamonds and found that they expand when irradiated with red laser light. The wavelength and intensity of the irradiation parameters were identical with the parameters used in the treatment of wounds. Sommer explains: "Nanoscopic water layers change their molecular structure, i.e. their density and viscosity, when exposed to laser light. They expand. When the laser is switched off, the water layers then contract again." The researchers translated this knowledge into living cells in the hope that something similar would happen, i.e. that the laser light would push the water out of the cells and that the cells would suck in water and other molecules from their surroundings when the laser is switched off.

Results obtained by researchers at the Karlsruhe Institute of Technology (KIT) led Sommer and his team to hope that the combined use of 670 nm laser light and green tea extract would remove neurotoxic amyloid beta deposits in the neuroblastoma cells. The KIT researchers had shown that the irradiation of human cancer cells with 670 nm laser light led to the uptake of elevated quantities of EGCG from the culture medium.

Hypothesis: light induces autophagocytosis

The cytostatic effect of EGCG is well known. The researchers from Ulm assumed that the amyloid beta peptides inside neuroblastoma cells are primarily degraded by light-induced autophagocytosis. If this were the case, it would be "highly interesting" because the success of transcranial light therapy used for the treatment of chronic traumatic brain damage could then potentially result from the same mechanism. It would also mean that light, in this case too, supports the degradation of tau protein aggregates, something that Andrei Sommer calls a "fascinating scenario". If intracellular tau tangles were degraded in vitro as a result of light-assisted autophagocytosis, this would then be important evidence for preventive strategies in some tauopathy cases.

"The results show numerous links with highly interdisciplinary scientific projects," confirmed Iris-Tatjana Kolassa, head of the Department of Clinical and Biological Psychology at the University of Ulm, going on to add, "the new combination of basic material science, psychology and medical research might in the future lead to completely new approaches to the treatment of age-related diseases such as Alzheimer's.

Besides Andrei Sommer, the project also involved the head of the Institute of Micro- and Nanomaterials at Ulm University, Hans-Jörg Fecht, and Dan Zhu, a scientist in Fecht's laboratory. The researchers from Ulm worked closely with researchers from the University of Heidelberg and from the Max Delbrück Centre for Molecular Medicine in Berlin. The project was funded by the Helmholtz Alliance for Mental Health in an Ageing Society (HelMA), the German Research Foundation (DFG) and the German Federal Ministry of Education and Research (BMBF).

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