

Malaria medication may help against one type of frontotemporal dementia

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Frontotemporal dementia is caused by a breakdown of nerve cells in the frontal and temporal region of the brain (fronto-temporal lobe), which leads to, among other symptoms, a change in personality and behavior. The cause of some forms of frontotemporal dementia is a genetically determined reduction of a hormone-like growth factor, progranulin. Scientists around Dr. Anja Capell and Prof. Christian Haass have now shown that various drugs that are already on the market to treat malaria, angina pectoris or heart rhythm disturbances can increase the production of progranulin. Accordingly, these drugs are good candidates for treatment of this specific form of frontotemporal dementia. The work will be published in the online edition of the scientific journal *Journal of Neuroscience* on February 2nd, 2011.

Progranulin is needed in the human [brain](#) as a protective factor for sensitive [nerve cells](#), too little progranulin therefore results in a progressive neuronal cell death. As for almost every other gene, there are also two copies of the progranulin gene in the cell. In patients with progranulin dependent frontotemporal dementia, one of the two copies is defective, leading to a 50% reduction in progranulin levels. To rescue the lack of progranulin, the Munich researchers tested various substances for their ability to stimulate the remaining progranulin production and identified a drug called bafilomycin (BafA1).

They then examined the [molecular mechanism](#) underlying the impact of BafA1 on progranulin more closely. Growth factors such as progranulin are produced in cellular membrane inclusions, known as vesicles. BafA1

has an alkalizing effect on these vesicles: After administration of BafA1 the interior of the vesicles is less acidic – and this increases the production of progranulin.

This observation encouraged the researchers to investigate further alkalizing substances for their ability to raise progranulin levels. Among the substances that passed the test were three drugs that are already on the market to treat various diseases: a medication for angina pectoris (bepridil), one for heart rhythm problems (amiodarone) and the widely used [malaria](#) drug chloroquine. Chloroquine increased the progranulin level not only in experiments with mouse cells to normal, but also in cells from patients with the defective progranulin gene.

In a clinical study in collaboration with the University of London, the team of Prof. Haass and Dr. Capell will now investigate whether chloroquine actually helps against progranulin dependent frontotemporal dementia. The human studies can be started very soon, as chloroquine has been used on countless patients, so that serious side effects are not to be expected. Even though the Munich scientists are optimistic, Prof. Haass warns against exaggerated hopes. "Experience shows that the step from cell and animal models to the patient is always connected with considerable difficulties. It will take several years until we know, whether chloroquine can be used as therapy for progranulin dependent frontotemporal [dementia](#)," says Haass.

More information: Capell, A., Liebscher, S., Fellerer, K., Brouwers, N., Willem, M., Lammich, S., Gijssels, I., Bittner, T., Carlson, A.M., Sasse, F., Kunze, B., Steinmetz, H., Jansen, R., Dormann, D., Sleegers, K., Cruts, M., Herms, J., Van Broeckhoven, C., Haass, C. (2011). Rescue of Progranulin Deficiency Associated with Frontotemporal Lobar Degeneration by Alkalizing Reagents and Inhibition of Vacuolar ATPase. *J. Neurosci.*, published online on February 2nd, 2011.

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