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Why HIV patients develop dementia: Researchers track harmful immune reactions in the brain

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Since the introduction of the combination anti-retroviral therapy (cART) in the mid-90s, the life expectancy of HIV patients has significantly improved. As a result, long-term complications are becoming more relevant: almost every second HIV patient is affected by neurocognitive disorders, which can lead to dementia. It has not as yet been fully understood how these disorders occur. Researchers from Bochum have now successfully identified mechanisms how infected cells can activate brain-specific immune cells which subsequently display harmful behaviour and lead to the destruction of neurons. These findings may help develop biomarkers to identify risk patients and to make a therapeutic strategy possible in the long term. The study was published in the trade journal *Experimental Neurology*.

"HIV-associated neurocognitive disorders" (HAND) include disorders of the cognitive functions, motor capacities as well as behavioural changes. How exactly HAND occur has not, as yet, been fully understood. "Scientists assume that HIV is harmful to cells directly and that is also triggers indirect mechanisms that lead to nerve cell damage," explains Dr Simon Faissner (RUB clinic for neurology, St. Josef-Hospital). The researchers strongly suspect that, once activated in the brain and the spinal cord, immune cells keep up a chronic inflammation level which then results in the destruction of nerve cells. An immune activation in peripheral tissue as well as therapeutic consequences may likewise contribute to nerve cell damage in the brain.

First steps of HIV infection are sufficient

The HI virus overcomes the blood-brain barrier hitchhiking on infected immune cells, the monocytes and probably the T cells. The researchers from Bochum tested the hypothesis that HIV-infected monocytes activate specific immune cells in the brain, the so-called microglial cells. These cells, in turn, respond by releasing harmful substances, such as reactive oxygen metabolites and inflammatory signalling molecules, i.e. cytokines. To test this hypothesis, the researchers developed a cell culture system in which they initially examined the effect of HIV-infected monocytes on microglial cells. The researchers simulated the individual steps of HIV infection and measured the volume of the cytokines released at each stage. Thus, they were able to demonstrate that releasing the viral RNA in the monocytes was a sufficient trigger for maximal microglial activation. Subsequent infection phases – reverse transcription into DNA and the resulting formation of HIV proteins – did not augment activation any further.

Released substances result in neuronal cell death

In the second step, they analysed nerve cells from rat brains to determine if the substances released by the microglial cells could lead to cell death. Compared with the control group, the number of cell deaths was indeed twice as high. Studies of liquor cerebrospinalis received from HIV-infected patients have shown a positive correlation with marker of neuronal degeneration in patients who did not as yet present any neurocognitive disorders.

Detailed understanding necessary for therapeutic strategies

"Thanks to our research, we have gained a better understanding of the

mechanisms of HIV-associated neurodegeneration," concludes Prof Dr Andrew Chan. "These results are likely to contribute to HAND biomarkers becoming established. In the long term, these data will be used to develop therapeutic strategies aiming at retarding HAND progression in HIV-infected patients." Starting points may include activation of microglial cells – a method that is applied in other autoimmune diseases of the central nervous system, for example in multiple sclerosis.

Start-up through FoRUM funds

The research, which was initiated following a collaboration between clinics for neurology and dermatology, St. Josef Hospital, as well as the Department for Molecular and Medical Virology, has been made possible through start-up funding provided by the Faculty of Medicine at Ruhr-Universität (FoRUM). The collaboration has evolved into an international consortium of clinics and basic research organisations in Bochum, Langen, Strasbourg and Mailand. One objective of the follow-up study, for which an application for EU funds is pending, is going to be an in-depth analysis of inflammatory processes in the central nervous system. The researchers will attempt to inhibit inflammatory processes with different drugs. They are, moreover, planning to study direct cell-cell interaction by means of state-of-the-art microscopy, in collaboration with the University of Strasbourg.

More information: Faissner, S. et al.: "Cytoplasmic HIV-RNA in monocytes determines microglial activation and neuronal cell death in HIV-associated neurodegeneration." In: *Exp Neurol*. 2014 Aug 19. pii: S0014-4886(14)00263-5. DOI: 10.1016/j.expneurol.2014.08.011. [Epub ahead of print],
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