Manipulating brain inflammation may help clear brain of amyloid plaques

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In a surprising reversal of long-standing scientific belief, researchers at the Mayo Clinic campus in Florida have discovered that inflammation in the brain is not the trigger that leads to buildup of amyloid deposits and development of Alzheimer's disease.

In fact, inflammation helps clear the brain of these noxious amyloid plaques early in the disease development, as seen from studies in mice that are predisposed to the disorder, say the researchers in the online issue of the FASEB Journal.

"This is the opposite of what most people who study Alzheimer's disease, including our research group, believed," says the study's lead investigator Pritam Das, Ph.D., an assistant professor in the Department of Neuroscience. "And it also suggests that we can take advantage of the brain's own immune cells by directing them to remove amyloid plaques from the brain, thus protecting the brain against their harmful effects."

The study tested the widely held belief that inflammation in the brain increases the production and buildup of a toxic protein known as amyloid beta (A?). Clumps of this protein in the brain are the hallmark pathological feature of Alzheimer's disease.

"The belief was that when the brain's immune cells, microglia, are activated following the initial buildup of amyloid plaques, the inflammation that ensues stimulates the brain cell's machinery to produce more A?, which then leads to more inflammation," Dr. Das says. "This chronic activation of immune cells results in a self-reinforcing feedback loop that promotes more and more A? deposition and inflammation, eventually leading to malfunction and death of brain neurons."

Although this notion, which came mostly from studies in laboratory cells, was accepted throughout the scientific community, the Mayo Clinic researchers developed a way to test it in a living organism — and they expected to see the same result.

"We had initiated these studies using our new in vivo model to confirm whether inducing inflammation in the brain would in fact exacerbate the disease," Dr. Das says.

The researchers used a technique known as "Somatic Brain Transgenesis" to increase expression of Interleukin-6 (IL-6), a cytokine that stimulates an inflammatory immune response in the brains of young mice predisposed to developing age-progressive amyloid plaques. This powerful technology allows researchers to express any gene of interest in specific parts of the body by tagging the gene onto Adeno-associated viruses, which are inert. In this way, they can study the function of any protein in the brain, and also test its potential therapeutic use.

They found that IL-6 triggered inflammation throughout the brain, and they expected to see a big buildup of plaque as well as damage to brain neurons. "Instead, to our surprise, we found that the inflammation prevented plaques from forming and cleared whatever plaque that was already there," Dr. Das says.

Given this unexpected result, they performed additional experiments using different strategies. "First, we expressed IL-6 in the brains of newly born mice that are yet to develop any amyloid plaques and, secondly, we expressed IL-6 in the brains of mice with pre-existing plaque pathology," he says. "In both these cases, we got similar results — the presence of IL-6 leads to the clearance of amyloid plaques from the brain."

The researchers then performed experiments to determine how the amyloid plaques were removed from the brain. Their analysis revealed that the inflammation induced by IL-6 in the brain directed

the microglia cells to remove the amyloid plaques from the brain. Microglial cells do this by phagocytosis. "They gobble up the plaque, which they 'see' as a foreign invader, and break it apart," Dr. Das says. Researchers also found that activated microglia cells were closely attached to the plaques and expressed proteins that help in removing the amyloid plaques from the brain.

Dr. Das hypothesizes that inflammation helps clear plaque early in the development of Alzheimer's disease, but that at some point, continued production of the amyloid clumps in the brain overwhelms the ability of microglial cells to do their job. At that point, inflammation, chronically activated by presence of the amyloid plaque, can produce its own unhealthy effects on brain function.

"Indeed, it may be feasible to transiently and selectively manipulate the microglia cells to alter amyloid plaques in a manner that is both effective and tolerable," he says. "However, given that chronic inflammation over years of insult may be detrimental, any intervention based on activation of the brain's immune system must clearly strike a balance between the neuroprotective and neurotoxic effects," cautions Dr. Das. "We need to study this phenomenon more thoroughly, but if we are right, it could have implications not only for Alzheimer's disease but also other neurodegenerative disorders characterized by protein buildup in the brain, such as Parkinson's disease."

Source: Mayo Clinic (news : web)