

In a paper just published in Cell Reports, Dena Dubal, Lennart Mucke, and their colleagues provide strong evidence that klotho enhances cognitive function, separate from its effects on aging. They started by looking at humans carrying an interesting variant of the KLOTHO gene. The variant was known to be associated with increased longevity, and the authors show that it leads to higher levels of klotho in the blood. Moreover, they show that carriers of the variant exhibit enhanced cognition, scoring higher on multiple tests of various aspects of cognitive function. The results suggest that systemic increases in klotho levels can improve cognitive function. So the authors took the experiments into mice. They found that elevation of klotho levels leads to improved learning and memory, seen in various tasks and shown not to be age-dependent. They went on to describe specific effects on synaptic function and plasticity that may account for the cognitive changes.

Our understanding of the protein, like Clotho, has changed through time: first described as a putative membrane protein with similarity to  $\beta$ -glucosidases, it is now known to be secreted (after processing by sheddases) and acts on both aging-dependent and -independent processes in organisms as different as mice and worms. Interestingly, accumulating evidence linked klotho to postnatal brain development, and mice with reduced klotho levels exhibited cognitive impairment.

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