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BIOLOGICAL SCIENCES

Parabiosis in aging research: Enigmatic youth factor versus ordinary stem cell transfusion effect

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ABSTRACT

Correspondence re: Villeda et al. 2014."Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice." *Nat Med* no. 20 (6):659-63. doi: 10.1038/nm.3569.

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Villeda and colleagues recently presented a supposedly experimental breakthrough, by connecting the blood circulatory systems of two mice - one old, and one young (=heterochronic parabiosis) - and found increased cognitive capacities and increased neuronal plasticity in the seniors (Villeda et al. 2014). In this study published in *Nature Medicine*, the authors concluded that some kind of soluble factor exists in the blood of young mice, which is capable of reversing age-related neuronal impairments in the brain. However, it seems that the authors did not perform a simple test to exclude the possibility of a cell transfusion effect.

Instead, in a different experimental setup, small groups of mice received multiple intravenous injections of old, young and heat-denatured blood plasma, which by definition is cell-free. However, since each group contained only 8 to 12 animals, and the changes in learning behaviors were within the range of 10-20%, the authors based their findings on the behavioral change of 1-2 mice. Considering the difficulty of measuring cognitive capabilities in rodents, these numbers are clearly non-significant, which leaves us with the histological and gene expression findings of increased neuronal plasticity in the hippocampus of old mice after heterochronic parabiosis (Villeda et al. 2014).

It has been known for some time that adult stem cells circulate in the blood of mammals and migrate into the tissues of several organs, including the brain (Mezey et al. 2000, Brazelton et al. 2000). Lifelong tissue regeneration seems to require the immigration of stem cells from the bloodstream (Borue et al. 2004), since the replicative potential of local tissue stem cells is limited, possibly due to telomere erosion (Sahin and Depinho 2010). A rejuvenation effect of young monocytes on the aged central nervous system during heterochronic parabiosis has been previously described (Ruckh et al. 2012). As a consequence, if one connects the blood circulatory systems of two mice, one must check for migrating stem cells, which could be the source of the rejuvenation effect on the brains of old mice.

Let me just add here that I disapprove of experiments like parabiosis, since human suffering from diseases can never be an ethical basis for this kind of torture of cognitive animals. However, since the damage is already done, I hope that the authors established heterochronic parabiosis between two mice of different sexes, e.g. a young male and a female senior mouse. If feasible, FISH should be performed on slices of hippocampal tissue from the old female mouse with a centromere probe of chromosome Y. To differentiate from immigrating blood cells (from the young mouse), an antibody labelled against a neuronal cell marker should be applied. If my concerns are correct, pairings of Y and neuronal cell marker signals will be found in the tissue sample of the old female.

In summary, the enigmatic youth factor might possibly be just a cell transfusion effect, namely the migration of adult stem cells with long telomeres from the young to the old mouse. Adult stem cells of young individuals have been shown to have higher regenerative capacities (Sahin and Depinho 2010). Circulating stem cells are directed by chemokines (Ponte et al. 2007), and aged tissues in old mice are expected to send desperate cries for "regenerative help", which might be answered by young stem cells from the other side of the parabiosis. If shown to be correct, this would add further support to the telomere theory of aging.

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APPENDIX

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