MedicalXpress

When the evil assumes power: On the dominance of stem cell mutations in age

June 5 2015

Aging is characterized by a decrease in regenerative capacity and organ maintenance as well as an increasing risk of cancer which coincide with mutations in stem and progenitor cells. In a working paper, researchers of Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI), Jena/Germany, University of Glasgow, UK, and Buck Institute for Research on Aging, USA, summarize and contrast international research results on the various cell-intrinsic mechanisms that lead to a clonal dominance of mutant stem and progenitor cells in aging tissues. The review will be published in the journal *Cell Stem Cell* on June 4th.

The incidence of tissue dysfunction, diseases and many types of cancer exponentially increases above the age of 45, showing a growing number of mutant stem or progenitor clones in the hematopoietic system, and the intestinal epithelium. New research results indicate that an increasing number of mutations in tissue stem cells are the main reason for carcinogenesis in age, starting years before the disease occurs. However, the mechanisms that initiate stem cell mutations and lead to their clonal dominance are poorly understood. Researchers from renowned age and cancer research institutes in Jena/Germany (Fritz Lipmann Institute (FLI)), Glasgow/UK (Beatson Institute for *Cancer Research*) and Novato/USA (Buck Institute for Research on Aging) now compiled and presented existing research results in order to show new approaches for the explanation of this dominance.

In general, the review shows that an increase of clonal dominance of mutant stem cells depends on the kind of tissue, the organism type as

well as on which mutations occur and which pathways are affected. For example, the effects of replication stress and telomere shortening in the human hematopoietic system are stronger than in the intestinal epithelium. In mice, there is no dependency between the clonal dominance of mural mutant intestine stem cells and the mice's growing age. Further, the clonal dominance of mutant stem cells can be context dependent, e.g. occurs in the context of intestinal inflammation but not in the non-inflamed intestine. It's a challenge for prospective research to find tissue-specific antecedents and consequences of cell mutations, especially with regard to the increasing dominance of mutations during aging.

Furthermore, the research experts highlight the loss of stem cell quiescence, replication-associated DNA damage, telomere shortening, epigenetic alterations, and metabolic challenges as determinants of stem cell mutations and clonal dominance in aging.

"There's a wide variety of reasons for the clonal dominance of mutant stem cells, and research is still in the beginning", Prof. Dr. K. Lenhard Rudolph, Scientific Director of FLI, resumes. "But we have to attach a high importance to this new research field regarding the development of therapies that aim to improve health in age. If we succeed to identify the antecedents of mutant stem cells' dominance in age, these processes can be targeted and diminished, thus leading to a lower risk of cancer and disease in our later years."

More information: "Aging Induced Stem Cell Mutations as Drivers for Disease and Cancer." *Cell Stem Cell* 2015, doi: dx.doi.org/10.1016/j.stem.2015.05.002.

Provided by Leibniz Institute for Age Research