Commentary

Stem Cell INVESTIGATION

Stem cells for all ages, yet hostage to aging

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In a tour de force, Rusty Gage and colleagues (1) showed that aging transcriptional changes in fibroblasts (FB) were reversed in induced pluripotent stem cells (iPSCs) derived from donors across the lifespan. Subsequently, when iPSCs were induced to form neurons by direct induction (iNS), the aging transcriptional signature was also absent. In contrast, when aging FBs were directly programmed to iNS by a similar protocol, they maintained an aging transcriptional signature. Remarkably, much of this signature was not the original signature of the FBs but a new age-associated signature more closely allied to neural related gene action. Thus, FB-derived iNS retained an "aging state" on direct cell programming, but not a hard wired, age-related transcriptional signature.

The potential for FB rejuvenation extends to 'senescent cells': from the same 74 years old, iPSCs were derived from either primary FBs or replicatively senescent FBs after serial *in vitro* passaging: both differentiated into normal embryonic lineages (2). Surprisingly, given the huge attention to regulatory mechanisms underlying iPSC generation (3), there has not been extensive comparison of iPSCs by donor age.

How do pre-existing problems such as DNA-damage relate to these processes? Mutations accumulate in aging skin as in all other mammalian tissues (4). Primary FBs from breast skin of donors aged 20–70 showed exponential increases in double-strand DNA breaks (histone marker ϒH2AX) against a linear doubling of chromosome structural abnormalities, 10% to 20% across the adult lifespan (5). Are their corrective mechanisms as part of the reprogramming process, and if so, how do these work?

Alternatively, reprogramming may select against damaged cells within a mixed cell population, which might be estimated by the efficiency of reprogramming (not reported here). Future studies may define a threshold level of DNA damage that is permissive for iPSC generation. Mertens *et al.* (1) proposed that iPSC generation with extensive cell proliferation would "dilute any accumulated molecular damage" which could not occur during iNS generation under conditions that limited cell proliferation. While replicative processes may weed out protein damage, it is not clear how these would remove DNA damage. As well as selecting against damage to nuclear DNA, selection is also likely for mitochondrial function. Lapasset *et al.* (2) showed remarkable mitochondrial rejuvenation in iPSCs generated from aging donors.

The age-related transcriptional signature observed in FB-derived iNS on direct neural programming was only evident in a donor group >40 years of age. There was minor overlap (4%) in the transcriptional signature of the 202 differentially expressed genes in iNS with the original FBs. Thus, the bulk of differentially expressed genes are new. Gene ontology analysis identified links with neural related functions including Ca^{2+} homeostasis, neural projection, and synaptic plasticity. Examining pre-frontal cortex (PFC) biopsies from autopsied brains across an age-spectrum identified a 7-fold greater overlap with the acquired iNS associated signature. This result could be interpreted as demonstrating a greater similarity of neural aging signatures *in vivo* with those in iNS *vs.* FBs. However, these results could simply reflect the expected differences in random sampling amongst different pool sizes for each set of differentially expressed genes. The size of the differentially expressed aging PFC gene pool is not well defined.

Of much interest to basic mechanisms in aging, Mertens *et al.* (1) identified RANBP17 as a new marker and potential

regulator of aging processes. RanBP17 is a protein of the ever-more-complex nuclear pores which mediates transport of proteins carrying nuclear localization signal peptides. RANBP17 levels were lower in FB from older donors. Aging is also associated with a less robust nucleo-cytoplasmic compartmentalization of proteins. Both nuclear import and nuclear export appear to become less selective during aging. In reprogrammed iPSCs the fidelity of these processes was restored, indicative of a "rejuvenation" of nuclear-cytoplasmic regulatory processes. Strikingly, in young FB, RanBP17 knockdown created an aging-like imbalance in nucleo-cytoplasmic sorting. These findings extend evidence that nuclear pore proteins have very long lifespans in various cells of mammals and worms, and that in aging mouse brain, Nup153 accumulates carbonyl groups associated with nuclear leakiness (6).

Cell aging as a target has distinct advantages for disease modeling, where age is clearly important, and for drug screening, where disease-relevant aged cell models may be more effective in identifying disease-fighting drugs. How might age be incorporated into these assays? The implication from the current work is that direct cell programming of FBs to cell-types-of-interest could be used to address age-related outcomes. Aging, where pathological processes are at play, is clearly distinct from the normal maturation of many cell types that occurs from the fetus to the adult. Is the acquisition of mature cell phenotypes (rarely obtained on differentiation of iPSCs even after extended culture), augmented by directed differentiation from mature FB? Interestingly, truncated lamins of the nuclear envelope associated with accelerated human aging in progeria patients, accelerate maturation of iPSC-derived dopaminergic neurons (7). Directed cell maturation and cell aging will enhance therapeutic uses of iPSCs.

The findings of Mertens *et al.* (1) have broad ramifications for the field of regenerative medicine. Whatever the mechanisms at play, the loss of aging signatures in iPSCs is good news for autologous iPSC directed-cell therapies where the aging population will be the major target for personalized regenerative medicine. However, while iPSCs and their direct derivatives may be rejuvenated, the host's aging environment is problematic. For example, grafts of embryonic neurons into older Parkinson patients show donor cells acquire features of diseased host neurons (8). Inflammation related to Alzheimer disease, and to basic aging itself, can also attenuate grafted stem cell function (9). Thus, prospects for rejuvenation by iPSC may still remain hostage to the aged host.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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