EDITORIAL

Gerogenes and gerosuppression: the pillars of precision geromedicine

Cell Research (2024) 34:463–466; https://doi.org/10.1038/s41422-024-00977-6

Tumorigenesis is driven by the gain-of-function mutation or overexpression of oncogenes, as well as by the inactivation of oncosuppresssive (tumor suppressor) genes due to their loss-of-function mutation, genomic loss, or epigenetic silencing. This combination of factors increases the cell-intrinsic fitness of malignant cells, enhances their capacity to obtain trophic support by the tumor microenvironment, and simultaneously subverts cancer immunosurveillance.[1] Since the realization that neoplasia is driven by molecularly defined genetic alterations, cancer is not more conceived as a fatality but as a disease that — at least theoretically — can be targeted by inhibiting oncogenes or reestablishing oncosuppression within the realm of 'precision oncology'. Indeed, at the oncological ward, deep sequencing of tumor DNA and RNA has become part of the clinical routine to retrieve information on genomic, epigenomic, and transcriptomic alterations and hence to identify patients who may benefit from specific drugs targeting relevant pathways.[2]

By analogy to this cancer-relevant process, we propose here that gerogenesis (aging) is driven by gerogenes (i.e., genes that favor the aging process) and facilitated by the failure of gerosuppressive genes and processes (which should inhibit aging), though with the difference that such genes and processes do not act in a cell-autonomous fashion but rather affect the system properties of the organism, thereby eroding general health[3,4] and precipitating a loss of body-wide fitness aggravating several or all of the hallmarks of aging.[5] The theoretical and clinical implications of this kind of reasoning are the same as for oncology because they might contribute to the advent of 'precision geromedicine'. The definition of genes as gerogenes or gerosuppressors is based on two criteria, namely, (1) polymorphisms, mutations, or other alterations in the genes/pathways should be associated with changes in human healthspan or lifespan, and (2) experimental gain-of-function or loss-of-function manipulation of the genes/pathways should yield phenotypes affecting healthspan and lifespan in animal models that include both accelerated aging (for the activation of gerogenes or the inactivation of gerosupressors) and decelerated aging (for the inhibition of gerogenes or the amplification of gerosuppressors). To date, this set of requisites is met by several gerogenes and gerosuppressors that affect different facets of the aging process (Fig. 1a).

EXAMPLES OF GEROGENES

APOE ε4

This apoliprotein E (*APOE*) gene variant, which is rarely encountered in centenarians, represents the ancient version of the *APOE* gene that, in contrast to its more modern alleles (*APOE* ε2 and *APOE* ε3), favors the accumulation of fat deposits during periods of food abundance and hence constitutes a 'thrifty' allele that was advantageous in primitive hunter-gatherer societies.[6] However, in modern societies, individuals carrying two *APOE* ε4 alleles are at an elevated risk for arteriosclerosis and Alzheimer's disease, especially if they consume a Western diet. This effect can be attenuated by the Mediterranean diet. Thus, the healthspan and lifespan of Southern Italians who emigrated to the US is impacted by *APOE* ε4, while that of Southern Italians who remained in their region of origin was scarcely influenced.[7] These findings underscore the importance of genotype–environment interactions for human aging, as well as the possibility to intervene on patients carrying two *APOE* ε4 alleles by dietary interventions.

IGF1

Loci associated with the insulin growth factor 1 (*IGF1*) pathway are associated with age-related traits.[8] IGF1 stimulates growth at a young age (its constitutive deficiency causes dwarfness and organ atrophy) but accelerates aging at an old age by excessive trophic signaling via mTORC1 through a pathway that can be intercepted by autophagy induction, thus illustrating the principle of antagonistic pleiotropy.[9] Moreover, the relationship between serum IGF-1 and age-related disease in older individuals is reportedly U-shaped, meaning that both high and very low IGF-1 levels are associated with detrimental outcome.[10] Hence, relevant genotyping and measurements of IGF1, its endogenous antagonists (IGF1 binding proteins), its upstream inducer growth hormone, and its downstream effectors might spur personalized interventions on IGF1 and its receptor IGF1R, both of which are druggable using monoclonal antibodies and specific small-molecule tyrosine kinase inhibitors, respectively.

LMNA

In the rare Hutchinson–Gilford progeria syndrome (HGPS), a de novo point mutation in *LMNA* (which codes for prelamin A) activates a cryptic splice site that results in a 50-amino acid truncation (Δ50aa) that encompasses the ZMPSTE24 cleavage site, resulting in a truncated and permanently C-terminally farnesylated mutant form of LMNA, termed progerin.[11] HGPS-associated progerin expression results in a variety of cellular defects including nuclear shape abnormalities, heterochromatin loss, DNA damage, proliferation defects, and cellular senescence, thereby driving a premature aging phenotype (alopecia, lipodystrophy, skeletal abnormalities, arteriosclerosis) that manifests in the second year of life and leads to death from cardiovascular disease at a mean age of 14 years. The sole FDA-approved treatment for HGPS patients is the farnesyltransferase inhibitor, lonafarnib.[11] Of note, HGPS leads to the overactivation of the nutrient sensors EP300 and mTORC1, thereby inhibiting autophagy.[12] Nutritional or pharmacological

Received: 9 May 2024 Accepted: 11 May 2024
Published online: 27 May 2024

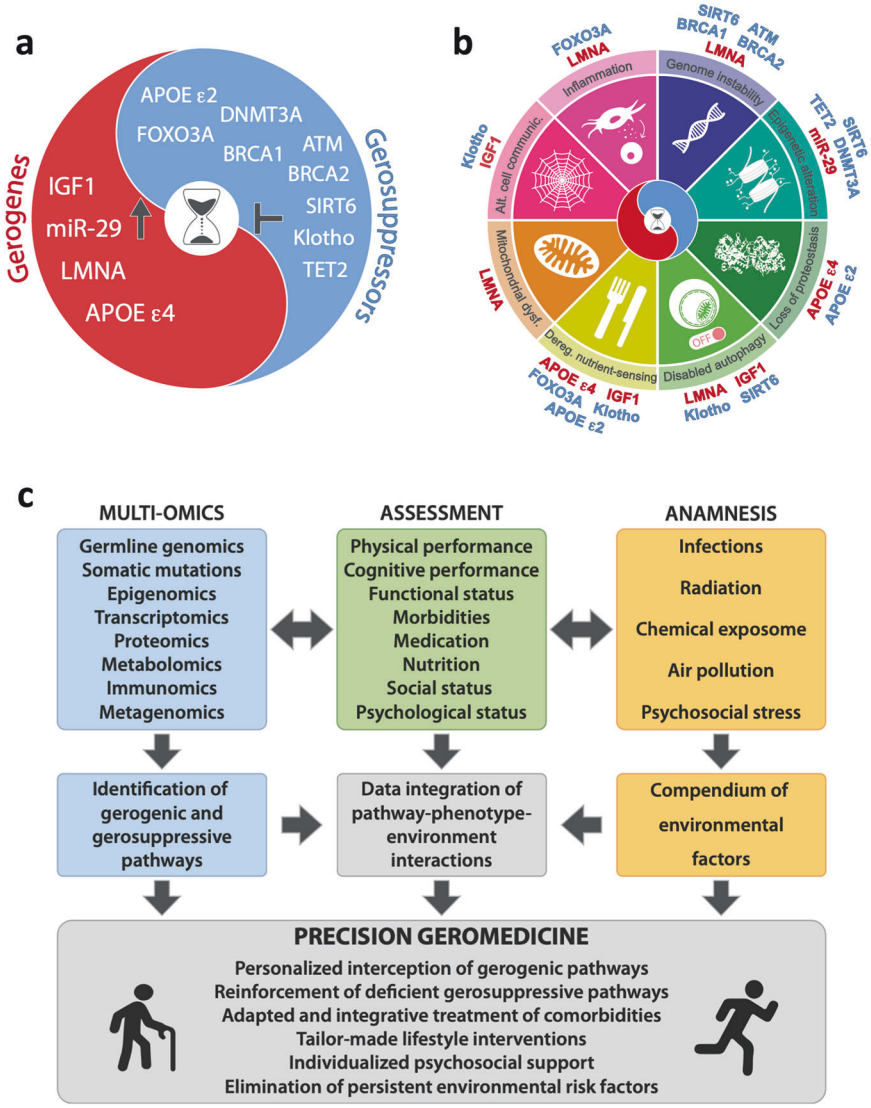

Fig. 1 The pillars of precision geromedicine. a Examples of gerogenes and gerosuppressor genes are inscribed into a Yin and Yang diagram. **b** Contributions of such gerogenes and gerosuppressor genes to selected hallmarks of aging are depicted. **c** Schematic representation of the principles of precision geromedicine.

activation of autophagy or mitophagy (which is mitochondrion-specific autophagy) can delay HGPS in mouse models.[13,14] It appears that both prelamin A and progerin contribute to non-syndromic aging (outside of HGPS) as well,[15] calling for diagnostic tests to measure their abundance and then to appropriately treat the affected subpopulation of patients.

NON-CODING RNAS

Among non-coding RNAs, several microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) may modulate the aging process.[16] For example, *miR-29* is upregulated during both normal and pathological aging in human and mouse tissues. Deletion of *miR-29* extends lifespan of progeroid mice, while *miR-29* overexpression in normal mice drives aging-related phenotypes including cell senescence, alopecia, osteoporosis, kyphosis and premature death. Other miRNAs (such as *miR-34a* that contributes to cardiac aging) and lncRNAs (such as *CDKN2B-AS1*, which has been linked to reduced paternal lifespan, type 2 diabetes, coronary artery disease, and cancer) are currently under close scrutiny.[16]

EXAMPLES OF GEROSUPPRESSOR GENES

APOE ε2

The protective *APOE* ε2 variant can be viewed as a gerosuppressor gene because its gene therapeutic expression in the ependyma reduces microglial activation, amyloid β plaque deposition, and neurodegenerative synaptic loss in a mouse model of Alzheimer's disease despite continued expression of human APOE ε4.[17]

DNA repair genes

ATM was the first gene to be associated with a hereditary progeroid syndrome, ataxia telangiectasia, which is due to a failure to repair DNA. Other progeroid syndromes (such as Bloom syndrome and Werner syndrome) are also due to loss-of-function mutations in DNA repair genes.[18] Accordingly, in the general population, acquired protein-truncating mutation in *ATM* and two other DNA repair genes (*BRCA1* and *BRCA2*) are negatively associated with lifespan.[19] Of note, deep sequencing of DNA from circulating leukocytes has revealed that semi-supercentenarians (age 105–109) or supercentenarians (age ≥ 110) exhibit signs of efficient DNA repair with a low load of somatic mutations.[20]

Hence, in theory, stimulation of DNA repair might constitute a strategy for delaying the aging process.

FOXO3A

FOXO3A encodes a transcription factor that acts in a nutrient-sensing pathway downstream of insulin and IGF1, and its rs2802292 G-allele is associated with longevity, especially in men.[21] This effect may result from enhanced functionality and reduced pro-inflammatory cytokine production and inflammaging.[22]

Klotho

The human klotho (*KL*) gene was originally identified as a gerosuppressor gene that encodes the α-klotho multifunctional protein. Plasma levels of α-klotho decrease during aging in humans. In mice, *KL* knockout shortens lifespan, while the *KL* overexpression extends longevity. Low-dose injections of α-klotho increase synaptic plasticity in mice and improve cognition in aged nonhuman primates.[23] These studies suggest α-klotho supplementation as part of pro-longevity strategies.

Non-coding RNAs

Several miRNAs and lncRNAs have been proposed as gerosuppressors.[16] For example, *miR-17* overexpression inhibits cellular senescence and insulin/IGF1 signaling to extend lifespan in mice, while *TERC* and *TERRA* lncRNAs contribute to telomere maintenance and extend longevity. Likewise, *Norad*-deficient mice exhibit premature aging, with increased genomic instability and mitochondrial dysfunction.[16] Nevertheless, further work will be necessary to validate the gerosuppressive relevance of these non-coding RNAs.

SIRT6

A *Sirtuin 6* (*SIRT6*) allele containing two linked substitutions (N308K/A313S) dubbed as centSIRT6 is enriched in Ashkenazi Jewish centenarians. These amino acid substitutions confer reduced deacylase and enhanced mono-ADP ribosyl transferase activity to centSIRT6 (compared to wild-type SIRT6), which is coupled to several functional improvements that may explain the longevity effects: stronger suppressor of LINE1 retrotransposons, elevated stimulation of DNA double-strand break repair, enhanced killing of cancer cells, as well as stronger interaction with, and ribosylation of, LMNA.[24]

TET2 and DNMT3A

Truncation mutations of *TET2*, an epigenetic modifier, are negatively associated with human lifespan.[19] Loss-of-function mutations affecting TET2 and another epigenetic modifier, DNMT3A, are among the most frequent ones observed in clonal hematopoiesis of indetermined prognosis (CHIP), a condition that becomes ever more frequent in old age and may contribute to leukemogenesis and inflammaging, hence enhancing the risk of non-small cell lung cancer and atherogenesis.[25]

The aforementioned gerogenes and gerosuppressor genes have all been involved in the human aging process and are connected to the hallmarks of aging (Fig. 1b). It is reasonable to expect that careful genotyping of such genes, as well as quantitative measurements of the pathways that they affect, will reveal associations with different phenotypic characteristics of aging.[18] This implies that distinct combinations of mutations or alterations in the expression levels affecting known and yet-to-be-discovered gerogenes and gerosuppressor genes — which likely interact to determine traits in a highly polygenic fashion — should be linked to the preferential manifestation of different age-associated diseases, including, but not limited to, cancer, cardiovascular disease, chronic inflammatory affections, immune defects, musculoskeletal disorders, neurodegeneration, and sensory disorders. Inversely, it appears plausible, but remains to be explored, that gene variants that have been associated with specific age-associated diseases (such as, for example, Alzheimer's disease, atrial fibrillation, cataract or hearing loss) have a broader impact on manifestations of aging than it has previously been suspected.[26] Hence, careful genotype-phenotype correlation analyses are required to pinpoint risk factors for specific age-associated diseases and to guide the interruption of disease-precipitating pathways with specific interventions that will constitute the armamentarium of precision geromedicine and extend human healthspan.

It can be argued that germline genetics determine human longevity to a larger extent at very old ages (> 100) than at younger ages when environmental factors play a preponderant role.[7] Indeed, for assessing the pace of aging and disease-predisposing factors, precision geromedicine should not only focus on germline alterations, but also identify somatic mutations linked to gerogenesis (such as those identifiable by deep sequencing of DNA from circulating monocytes resulting in the quantitation of CHIP). Such somatic mutations could also be measured in biopsies derived from internal organs, as this has been documented for esophageal epithelia and many other tissues.[27] In addition, precision geomedicine should aim at characterizing epigenetic alterations (that can be captured by bisulfite sequencing and algorithms measuring epigenetic 'clocks'), coding and non-coding RNAs, post-genetic changes (that can be measured by plasma proteomics and mass spectrometric metabolomics, phenotypic characterization of circulating leukocytes or 'immunomics', fecal metagenomics, magnetic resonance imaging and metabolomics of internal organs, etc.), as well as full clinical and digital assessments that involve the combined evaluation of physical and cognitive performance, functional status, morbidities, medication use, nutrition, social support and psychological status.[28] Ideally, careful anamneses should identify environmental clues including infections, radiation, exposure to chemicals, air pollution, and psychosocial stress. Such an integrated approach would transcend the aforementioned genotype-phenotype correlation analyses by retrieving non-genetic molecular information, as well as knowledge of exogenous risk factors (Fig. 1c).

One final fascinating point concerns the interaction between gerogenesis and oncogenesis. While some gerogenes (e.g., *IGF1*) but not others (e.g., *APOE* ε4, *LMNA*) also have oncogenic effects, it appears that most of the gerosuppressor genes are endowed with oncosuppressive activity. This relationship may be inscribed in the well-established epidemiological association between old age and cancer. However, this association is imperfect in thus far that — paradoxically — very old age (≥ 90 years) is associated with a progressive reduction in the incidence of new cancer diagnoses.[29] It remains to be determined whether this latter effect reflects genetic variations — and perhaps environmental factors — that not only drive 'successful' aging but also reduce the probability of carcinogenesis and tumor progression.

Carlos López-Otín[1,2], Andrea B. Maier[3,4,5] and Guido Kroemer[1,6,7]✉

[1]*Centre de Recherche des Cordeliers, Equipe labellisée par la Ligue contre le cancer, Inserm U1138, Université Paris Cité, Sorbonne Université, Paris, France.* [2]*Facultad de Ciencias de la Vida y la Naturaleza, Universidad Nebrija, Madrid, Spain.* [3]*Department of Human Movement Sciences, @AgeAmsterdam, Faculty of Behavioural and Movement Sciences, Vrije Universiteit, Amsterdam Movement Sciences, Amsterdam, the Netherlands.* [4]*Healthy Longevity Translational Research Program, Yong Loo Lin School of Medicine, National University of, Singapore, Singapore.* [5]*Centre for Healthy Longevity, @AgeSingapore, National University Health System, Singapore, Singapore.* [6]*Metabolomics and Cell Biology Platforms, Gustave Roussy Institut, Villejuif, France.* [7]*Institut du Cancer Paris CARPEM, Department of Biology, Hôpital Européen Georges Pompidou, AP-HP, Paris, France.* ✉*email: kroemer@orange.fr*

REFERENCES

1. Swanton, C. et al. *Cell* **187**, 1589–1616 (2024).
2. Wahida, A. et al. *Nat. Rev. Cancer* **23**, 43–54 (2023).
3. Lopez-Otin, C. & Kroemer, G. *Cell* **184**, 1929–1939 (2021).
4. Lopez-Otin, C. & Kroemer, G. *Cell Stress* **8**, 21–50 (2024).
5. Lopez-Otin, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. *Cell* **186**, 243–278 (2023).
6. Neel, J. V. *Am. J. Hum. Genet.* **14**, 353–362 (1962).
7. Caruso, C. et al. *Int. J. Mol. Sci.* **23**, 5635 (2022).
8. Teumer, A. et al. *Aging Cell* **15**, 811–824 (2016).
9. Abdellatif, M., Madeo, F., Sedej, S. & Kroemer, G. *Expert Opin. Ther. Targets* **27**, 87–90 (2023).
10. Zhang, W. B., Ye, K., Barzilai, N. & Milman, S. *Aging Cell* **20**, e13443 (2021).
11. Misteli, T. *Cell* **184**, 293 (2021).
12. Son, S. M., Park, S. J., Breusegem, S. Y., Larrieu, D. & Rubinsztein, D. C. *Nat. Cell Biol.* **26**, 235–249 (2024).
13. Ferreira-Marques, M. et al. *Aging Cell* **22**, e13983 (2023).
14. Sun, Y. et al. *Aging Cell*, e14143 (2024).
15. Primmer, S. R., Liao, C. Y., Kummert, O. M. P. & Kennedy, B. K. *Aging* **14**, 8150–8166 (2022).
16. Ugalde, A. P. et al. *J. Gerontol. A Biol. Sci. Med. Sci.* **79**, glae058 (2024).
17. Jackson, R. J. et al. *Mol. Ther.* **32**, 1373–1386 (2024).
18. Worm, C. et al. *Aging* **16**, 2026–2046 (2024).
19. *Nat. Aging* **2**, 285–286 (2022).
20. Garagnani, P. et al. *Elife* **10**, e57849 (2021).
21. Revelas, M. et al. *Mech. Ageing Dev.* **175**, 24–34 (2018).
22. Torigoe, T. H. et al. *NPJ Aging* **10**, 18 (2024).
23. Castner, S. A. et al. *Nat. Aging* **3**, 931–937 (2023).
24. Simon, M. et al. *EMBO J.* **41**, e110393 (2022).
25. Jaiswal, S. & Libby, P. *Nat. Rev. Cardiol.* **17**, 137–144 (2020).
26. Liu, T. et al. *J. Prev. Alzheimers Dis.* **11**, 196–213 (2024).
27. Li, R. et al. *Nature* **597**, 398–403 (2021).
28. Bonnes, S. L. R. et al. *Geroscience* https://doi.org/10.1007/s11357-024-01132-0 (2024).
29. Lopez-Otin, C., Pietrocola, F., Roiz-Valle, D., Galluzzi, L. & Kroemer, G. *Cell Metab*. **35**, 12–35 (2023).

COMPETING INTERESTS

G.K. is member of the scientific advisory boards of Hevolution and Rejuveron. G.K. is cofounder of four biotech companies (everImmune, Osasuna Therapeutics, Samsara Therapeutics, Therafast Bio.) that target age-related diseases. ABM is co-founder of Chi Longevity, a private longevity clinic, and Chief Medical Officer of NU, a biotechnology research company.