AGEING

Loss of gene coordination as a stochastic cause of ageing

A new global measure of cell-to-cell transcriptional variability from single-cell RNA-sequencing data has been developed by Levy et al., on the basis of the transcriptional interrelations between genes. The new variable, termed global coordination level, decreases with age in different organisms and cell types and correlates with high mutational load in cells.

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Ageing, the progressive fitness decline that brings life to a close, has been explained in evolutionary terms as a decline in the efficacy of natural selection with age[1]. However, the process has stubbornly escaped an explanation in terms of causality. In lieu of a clear cause-and-effect relationship to explain age-related functional decline and increased disease risk, the process has been discussed in terms of hallmarks of ageing, that is, age-related phenotypes that appear to be conserved among species[2]. Most hallmarks are adaptive responses, such as responses to stress exposure. Those are similar from cell to cell, because they represent evolutionary adaptations for optimal functioning over time in a continually changing internal and external environment. However, some hallmarks are stochastic and differ among cells. Because ageing has not itself been selected for a possible beneficial effect[1], the ultimate causes of ageing are non-adaptive and are likely to be stochastic in nature. Of course, multiple examples exist of adaptive changes that further contribute to age-related functional loss and disease, such as inflammation and various responses to stress exposure. However, these could be argued to not be the primary changes that drive the process.

Stochasticity is a general characteristic of living systems, which is evident at all levels of the molecular machinery that runs cells. An intriguing example of stochasticity in the functioning of cells is the random fluctuations in the levels of messenger RNAs, proteins and other biomolecules. Such noise, as it is often called, is inherent in molecular interactions, which are intrinsically stochastic, and has been co-opted by evolution for probabilistic regulation of gene activity, for example, during development, in cell-cycle regulation or as part of the immune response[3]. In particular, transcriptional noise, that is, different levels of mRNAs among otherwise-identical cells, has received attention since advances in genomics allowed for the measurement of transcript levels in single cells. Interestingly, several laboratories have now shown that transcriptional noise levels increase with age in different cell types in mice and humans[4–6], possibly as a consequence of the accumulation of mutations or and/or epimutations[7].

Measuring transcriptional noise levels through quantifying individual gene transcript levels across cells in single-cell RNA-sequencing ignores that genes do not operate in isolation but instead are connected in gene regulatory networks. In this issue, Levy et al.[8] present a clever new measure to cut across the network of interactions among genes and consider their transcriptional interrelationships. The new measure, called global coordination level (GCL), is based on the average multivariate dependency between the expression levels of random subsets of genes in single-cell RNA-seq datasets. A GCL of zero signifies

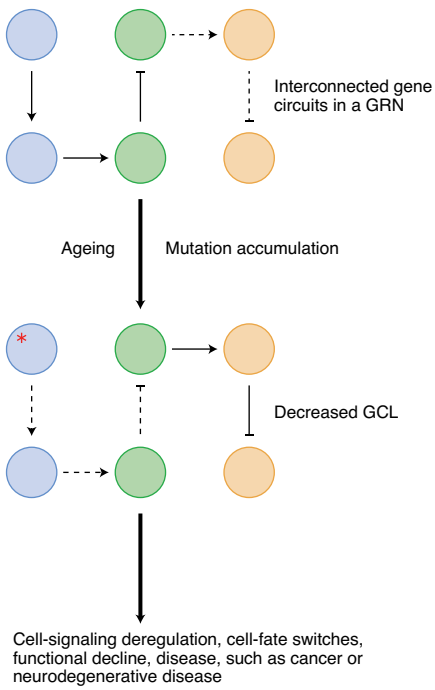

Fig. 1 | How mutation accumulation can lead to GCL decline. Schematic showing a highly simplified depiction of how even one somatic mutation could causally contribute to ageing by affecting transcriptional interrelations in GRNs in cells. The mutation (asterisk) in one gene or in one of its regulatory sequences decreases the number of strong interconnections from three to two. The mutation could be of any type, from a base substitution to a chromosomal aberration.

independent gene expression, whereas values above zero reflect gene-to-gene regulatory interactions. For example, when applied to known genetic pathways in the Kyoto Encyclopedia of Genes and Genomes database, the GCL was found to be significantly above zero, whereas genes completely randomized to mimic such pathways yielded GCLs of essentially zero.

When the authors then assessed GCLs in multiple single-cell RNA-sequencing datasets, they found that it consistently declined with age in different organisms and cell types. Interestingly, in single-cell RNA-seq data from mouse haematopoietic stem cells, the age-related decreases in GCL were found to be non-random, and some pathways were more susceptible to age-related decline than others. This finding may simply be random, owing to a small number of genes and/or regulatory elements being present in a pathway, but also may reflect the specific cellular function associated with that pathway. Indeed, it is far too early to rule out the possibility that inherently stochastic ageing processes could not have non-random, specific effects. The results of this study are consistent with the long-standing hypothesis of ageing as dysdifferentiation, that is, cells drifting away from their proper state of differentiation. Posited by Richard Cutler in the 1970s, the idea was based on observations of active genes in aged tissues that should normally be silent in that tissue[9].

An important facet of this work is the demonstration that increased mutations in tissues at old age appear to correlate with decreased GCL values (Fig. 1). Indeed, in a dataset on human pancreatic cells in which both mRNA levels and somatic mutations were assessed in the same cells[5], the cells with the highest mutational loads generally also had the lowest GCL values. Moreover, with another single-cell RNA-seq dataset, this time on radiation-exposed cells, the authors found a lower GCL in the cells exposed to a high radiation dose. Although a relationship between DNA damage and/or mutations with transcriptional noise has been suggested in previous studies, this evidence of a cause-and-effect relationship is the strongest to date.

These observations suggest that increased transcriptional noise is a potentially universal, stochastic hallmark of ageing driven by damage accumulation. Stochasticity has been found in many aspects of ageing, including large lifespan differences in isogenic worms or inbred mice kept in the same environment[10]. The development of GCL paves the way for further exploration of the possibility that a breakdown of gene expression coordination might underlie some of the extensive phenotypic variation in ageing and lifespan. As suggested by the authors, this finding may have translational relevance in the current explosion of new strategies for combating ageing. Practical ways to prevent or slow the relentless accumulation of stochastic damage in cells during ageing may be developed on the basis of measures such as GCL as biomarkers. ❐

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References

1. Kirkwood, T. B. *Cell* **120**, 437–447 (2005).
2. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. *Cell* **153**, 1194–1217 (2013).
3. Chalancon, G. et al. *Trends Genet.* **28**, 221–232 (2012).
4. Bahar, R. et al. *Nature* **441**, 1011–1014 (2006).
5. Enge, M. et al. *Cell* **171**, 321–330.e314 (2017).
6. Angelidis, I. et al. *Nat. Commun.* **10**, 963 (2019).
7. Vijg, J. & Dong, X. *Cell* **182**, 12–23 (2020).
8. Levy, O. et al. *Nat. Metabol.* https://doi.org/10.1038/s42255-020-00304-4 (2020).
9. Ono, T. & Cutler, R. G. *Proc. Natl Acad. Sci. USA* **75**, 4431–4435 (1978).
10. Martin, G. M. *Mech. Ageing Dev.* **133**, 107–111 (2012).

Competing interests

J.V. is a cofounder of and stock holder in SingulOmics, Corp., USA.