Omics technologies and the study of human ageing

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Abstract | Normal ageing is associated with diverse physiological changes in all organ systems but the rate and extent of these changes vary markedly among individuals. One aspect of ageing research focuses on the molecular profiling of the changes that occur with increasing age in humans. Such profiling has implications for disease prevention and treatment. New high-throughput 'omics' technologies (such as genomics, metabolomics, metagenomics and transcriptomics) are enabling detailed studies of these molecular changes and are thus revealing information about the biological pathways that change with age.

Ageing is a complex multifactorial process during which molecules, cells and organs undergo damage over time, resulting in loss of function, increased morbidity and, eventually, death[1]. Current knowledge of the molecular pathways involved in ageing has derived, to a large extent, from studies on lifespan and longevity in simple model organisms (for example, yeast and nematodes). Many of these pathways are conserved in mammals and may therefore be relevant to human ageing. The heritability of human lifespan is only around 25%[2], indicating that, to a large extent, lifespan is not genetically determined. This suggests that age-related mortality is likely to be influenced by the molecular changes over time that result from a combination of environmental, epigenetic, post-translational, microbial and lifestyle factors. The field of ageing research seeks the biological basis of physiological ageing, and the risk factors (molecular or otherwise) that lead to diversity in morbidity and lifespan[2].

Large-scale high-throughput technologies that allow genome-wide studies or those on large panels of markers — often referred to as 'omics' approaches — are making it possible to consider questions such as are age-related changes in DNA methylation constant over time and are there age-related gene expression changes common to all tissues? Mapping molecular changes with age is only a small component of unravelling the biology of ageing, but such omics studies in humans can assist the field and can help to derive biomarker profiles that can be used to predict and monitor age-associated physiological decline and disease. In this Progress article, we discuss the recent progress that has been made in applying these technologies to the molecular changes that are observed with human ageing. Existing theories on ageing are beyond the limited scope of this article. We also do not discuss the role of genetic variation in ageing or genomic studies of the pathways that determine ageing and longevity (reviewed in REF. 2).

> "New high-throughput 'omics' technologies are … revealing information about the biological pathways that change with age"

Some representative examples of omics studies are summarized in TABLES 1,2. In addition to a range of omics approaches, different study designs are needed to investigate human ageing in order to recognize molecular changes that are relevant to ageing, and some of these study designs can help to establish causal links (BOX 1).

Somatic mutations

Somatic mutations in humans, both in the nuclear genome and in the mitochondrial genome, have been implicated in ageing[3] for some time. Advances in genomic methods, such as next-generation sequencing and the use of single nucleotide polymorphism (SNP) arrays to genotype large numbers of individuals, have provided further insight into somatic mutations in the context of ageing. For example, two recent studies used data from genome-wide association studies (GWASs) (including data from >100,000 participants in total) to look at large structural abnormalities; the authors found that clonal mosaic karyotype anomalies become more frequent both with increasing age and in cancer[4,5].

In addition, studies using array-based SNP data or next-generation sequencing have shown increased accumulation of somatic mitochondrial DNA (mtDNA) mutations with increasing age[6] and age-related diseases[7]. All regions of the mitochondrial genome are affected[6] but these age-related changes are seen only in certain tissues and not across all age ranges[8]. Another study using deep sequencing showed that patients taking anti-retroviral drugs progressively accumulate somatic mtDNA mutations[9]. These patients display physiological changes that are similar to those seen in ageing, often leading to progressive multi-organ deterioration that is normally only seen much later in life. Such observations add weight to the idea that somatic mtDNA mutations have a role in the ageing process[9].

Transcriptomics

Transcriptomics — using microarrays and, more recently, RNA sequencing (RNA-seq) — has been used to study ageing for many years. Most transcriptomic studies try to identify genes that are differentially expressed with chronological age, mainly using cross-sectional study designs. To illustrate the range of tissues, platforms and sample sizes used, we have selected some examples of transcriptomic studies (TABLE 2). For human studies, it can be difficult to acquire adequate tissue for analysis, resulting in studies with small sample

Table 1 | **Examples of 'omics' studies of molecular changes with increasing age in humans**

Omics approach	Study design	Outcome measured	Tissue studied	Key findings	Refs
mtDNA somatic mutation detection using array-based genotyping	Cross-sectional; age range 0–60; mothers and offspring (*N* = 2,491)	mtDNA heteroplasmy	Blood	• Heteroplasmy is dynamic over the human lifespan, although some of it is inherited • Heteroplasmy increases with age	6
Genome-wide methylation using the Infinium 450k BeadChip arrays	Cross-sectional; age range 19–101 (*N* = 656)	Methylation fraction	Blood and multi-tissue validation	• Genome-wide methylation levels can predict over 90% of variance in chronological ageing; that is, an individual's variance can be predicted based on DNA methylation levels	28
Genome-wide methylation using bisulphite sequencing	Cross-sectional; comparing newborns (*N* = 19) to nonagenarians (*N* = 19)	Methylation levels	Blood	• There is an overall marked decrease of global methylation with extreme age, but CpG island promoter hypermethylation is still seen	22
Genome-wide miRNA analysis	Cross-sectional; comparing healthy long lived (mean age is 96; *N* = 15) to middle aged (mean age is 46; *N* = 55)	miRNA expression levels	Blood	• Several differentially regulated miRNAs are also altered in age-related diseases • Many potential targets of the downregulated miRNAs are in tumour suppressor pathways (for example, p53)	17
Metabolomic profiling using the Biocrates panel	Cross-sectional; age range 32–81 (*N* = 2,162)	Serum metabolite levels	Serum	• Levels of metabolites relating to incomplete mitochondrial fatty acid oxidation are strongly associated with age	33
Metabolomic profiling using the Metabolon panel	Cross-sectional; age range 20–82 (*N* = 6,942)	Serum or plasma metabolite levels	Serum and plasma	• 22 metabolites explain 59% of the variance in chronological age and are also associated with mortality • A novel metabolite, C-glyTrp, is also associated with age-related traits (lung function and bone mass) and birthweight, a known early developmental factor that affects health status in middle age and old age	35
Metagenome analysis of the gut microbiome by next-generation sequencing of 16S rRNA	Cross-sectional; elderly people (age range 64–102); comparing diet and health status (*N* = 178)	Metagenomic diversity and composition	Faeces	• Strong associations among diet, microbiota composition, inflammation and health status in old age	39

C-glyTrp, C-linked glycosylated tryptophan; miRNA, microRNA; mtDNA, mitochondrial DNA; rRNA, ribosomal RNA.

numbers and potentially limited power for discovery. Many of the studies with larger numbers have focused on blood, which is easily accessible[10]. This adds a layer of complexity to interpretation owing to the different cell types found in whole blood; it should also be considered that its cellular composition might change with age. Owing to this added complexity for transcriptomics and omics generally, the age-related changes observed in blood might not reflect those found in other tissues. Cell type heterogeneity may also affect the ability to discover variation in gene expression in other complex tissues such as the skin[10].

Some studies[11] have compared normally ageing individuals with younger patients with progeria syndromes and have found that the majority of age-related expression changes are similar in both. A recent meta-analysis of age-related gene expression profiles tried to identify common signatures of ageing across tissue and species[12]. Using experiments from mice, rats and humans, 73 genes were found to be consistently differentially expressed with increasing age. The gene with the greatest increase in expression was apoplipoprotein D (*APOD*), which is known to be associated with neurodegenerative diseases. The top genetic categories for altered gene expression with age were related to the immune response, including complement activation, antigen processing by the lysosome, apoptosis and anti-apoptosis pathways[12]. Many of the expression changes that have so far been found in studies of human blood have also been found in genes related to lymphocytes and the immune system[13]. Some studies of gene expression in blood from long-lived families have also implicated the mammalian target of rapamycin (mTOR) pathway as relevant to longevity in humans, which is consistent with findings in model organisms[14].

Another tissue that has been studied is the brain. For example, a study that sampled multiple sites in post-mortem brain sections demonstrated brain region-specific changes and changes in the expression of synapse-related genes[15]. Other changes, including the downregulation of mitochondrial genes, have been found across tissues[13]. The consensus is that gene expression changes with age are usually tissue-specific[16], although this may be a consequence of small sample sizes and a lack of study power.

Another challenge is replication, either due to the difficulty in finding other cohorts for which the same tissues are available or due to the use of different microarray platforms; the issue of platforms may be partly overcome by RNA-seq data. Current gene expression array data are also limited in that they do not provide information for microRNAs (miRNAs) for which different arrays are needed. Initial studies suggest a role for miRNAs in human ageing and longevity[17]. Although different preprocessing may be required, RNA-seq data can be used to detect miRNAs and will also help to overcome the lack of sensitivity to low abundance transcripts that is suffered by microarrays. RNA-seq can also provide information on splicing and allele-specific expression; studying the transcriptome at this increased level of detail is vital for

Table 2 | **Examples of transcriptomic studies in the context of increasing age in humans**

Tissue	Demographic	Sample size	Platform	Key findings	Refs
Kidney (normal tissue taken at nephrectomy for malignancy)	27–92 years	74	Affymetrix HG-U133A/B	• Altered expression of 985 genes with age, including increased expression of genes specific to immune cells, suggesting that immune surveillance or inflammation increases with age • Age-regulated genes showed similar profiles with age in the cortex and the medulla	44
63 abdominal wall muscle; 18 arm or leg muscle	16–89 years	81	Affymetrix 133 2.0 Plus	• 250 genes were differentially regulated in muscle; these were compared with age-related expression profiles in the brain and kidney • Common pathways upregulated with age were involved in the extracellular matrix, cell growth, complement activation and components of the cytosolic ribosome • Pathways involved in chloride transport and genes encoding subunits of the mitochondrial electron transport chain had decreased expression with age	16
Brain post-mortem samples	65–100 years	191	Illumina Human Ref Seq-8	• Mitochondrial related genes were downregulated with age in both tissues; many of the other changes were tissue specific • 54 genes changed expression with age in the brain, including the downregulation of genes related to synaptic function	13
Lymphocytes	15–94 years	1,240	Illumina Sentrix WG6	• Mitochondrial related genes were downregulated with age in both tissues; many of the other changes were tissue specific • 1,060 genes showed altered expression in lymphocytes, including increases in expression of genes related to immune responses	13
Four regions of 81 brain samples from individuals with Alzheimer's disease	74–95 years	26	Affymetrix HgU133 Plus 2.0	• Region-specific synapse-related genes showed progressive downregulation in normal ageing brains and in the context of Alzheimer's disease • Multiple aspects of synaptic function were affected, suggesting that the function of existing synapses might be impaired	15
Four regions of 81 brain samples from individuals with normal ageing	20 –90 years	55			
269 prefrontal cortex post- mortem brain samples	Fetal (14 weeks of gestation) to 80 years	269	Custom-microarray Illumina Oligoset 49,152 probes	• Gene expression changes occurring during fetal development were reversed in early postnatal life • Decades later, this pattern of reversal was mirrored in ageing and neurodegeneration	45
62 human sun-protected skin samples	18–75 years	31 males and 31 females	Affymetrix U133 Plus	• Sex- and species-specific patterns were seen with age • In females, the expression of transcripts associated with T cells, B cells and dendritic cells increased with age; these changes were opposite or absent in males • Pro-inflammatory gene expression changes were not seen in the mouse tail samples with age	46
30 mouse tail skin samples	5–30 months	15 males and 15 females	Affymetrix Mouse Genome 430		
Meta-analysis of 27 human, mouse and rat data sets using normal tissue	Four human studies, age range 20–106 years; 23 rodent studies, age range 3–30 months	>Three samples in each age group	Various	• Several common genetic signatures observed with age, including 56 genes with increased expression and 17 genes that were underexpressed • Genes with increased expression included some linked to inflammation and immunity; decreased expression of collagen genes and mitochondrial genes was reported with age, as well as changes in the expression of genes related to apoptosis, the cell cycle and cellular senescence biomarkers	12
705 abdominal skin samples; 825 abdominal fat samples; 825 LCL samples and 92 fresh lymphocytes	39–85 years	All females	Illumina Human HT-12 V3 BeadChips	• Studied gene expression changed with chronological age in multiple tissues from the same individual; results were compared with those from a brain cohort • Most age-related changes in gene expression were tissue-specific changes; the few genes that had changes in expression across tissues have roles in cell division, senescence or apoptosis	47
Ten regions of post-mortem brain samples	18–101 years	78 males and 22 females	Affymetrix Human Exon 1.0 ST array		

LCL, lymphoblastoid cell line.

Box 1 | **Some of the study designs used to investigate molecular ageing in humans**

Cross-sectional studies
A molecular measure (for example, gene expression) is obtained in a group of individuals of different ages. This can be done either within a given age range, to correlate the molecular measure with age, or in two different age groups (for example, young versus old). Most human studies of ageing that have been carried out so far fall into this category. These studies estimate changes with age from the differences between individuals of different ages and the results may be confounded by unknown inter-individual differences, thus resulting in inaccurate estimates of age-related changes.

Longitudinal studies
In these studies, either a molecular or a clinical trait is assessed for the same individual using at least two separate time points. This approach measures the molecular change with age. Prospective studies are costly and time consuming but represent the 'gold standard' to assess change over time and to overcome issues of confounding. Human longitudinal 'omics' studies have not yet been published but this approach is used for epidemiological research on ageing. This design has been applied to population-based studies of elderly individuals followed over many years and allows a molecular profile to be linked with subsequent morbidity or mortality. Longitudinal studies of nonagenarians and centenarians allow the detection of causal determinants of longevity at old ages.

Studies of longevity
These studies compare molecular profiles and health in long-lived individuals (for example, centenarians) to those in the general population. The aim is to understand the molecular changes found in those individuals who age well and enjoy a long life. Establishing which changes are causative and which are the result of ageing is not possible in cross-sectional studies. Many different study cohorts of centenarians currently exist and are being examined for a variety of omics measures. Challenges include a loss of study power as it is impossible to predict which controls (that is, members of the general population) will also be long lived. A subset in this category is offspring–spouse studies, which compare the molecular profiles in long-lived individuals to those in the general population, often in combination with a comparison of the offspring of long-lived parents and age-matched controls.

further understanding ageing[18,19]. Currently, RNA-seq protocols are not standardized and the full potential of this technology has not yet been ascertained. Importantly, a single level of omics data — such as transcriptomics — alone cannot indicate whether the changes discovered are causative or whether they are a result of ageing. Discriminating cause and effect would require the integration of multilevel genotypic, transcriptomic, epigenetic, proteomic and phenotypic data over time.

DNA methylation

Gene expression is modulated by epigenetic factors such as histone modifications and DNA methylation, and there is currently interest in examining DNA methylation during a life course. Technologies for DNA methylation analysis have made considerable progress and now allow high-throughput analyses. The choice between a sequencing-based or an array-based approach depends on the numbers of samples that need to be tested, the quality and quantity of DNA available, and the coverage and resolution that are required[20].

One of the first questions addressed has been whether DNA methylation is altered with age. Using Infinium BeadChip arrays made by Illumina (namely, Infinium 27k and Infinium 450k arrays), changes in DNA methylation have been shown to occur during both cellular senescence and *in vivo* ageing[21]. Most of the data generated to date are based on these arrays, which are biased towards gene promoters, and so the findings cannot be extrapolated to the whole genome. A study of whole-genome bisulphite sequencing compared cord blood from newborn infants with peripheral blood from centenarians and found an overall marked decrease in global methylation and CpG island promoter hypermethylation with extreme age, confirming findings from array studies[20]. However, this study also found that many of the methylation changes seen with age take place at repetitive DNA, which is not covered by the arrays[22]. So far, the main sites to be identified as showing altered methylation with age have been at the promoters of genes that have roles in development or that have known functions in cellular ageing in the brain and blood[21]. It should be noted that predetermined DNA methylation changes result in gene expression patterns that are important for differentiation and development, as well as stress responses (for example, infection), but random DNA methylation changes that occur over time or as a consequence of damage may also be correlated with age.

A cross-sectional study that looked at DNA methylation in paediatric (boys aged 3–17 years) and adult populations found age-associated changes at 2,078 of 27,000 loci[23]. Meta-analysis of age-associated DNA methylation changes in adult populations ($N = 1,158$) revealed that 74.0% of age-associated loci in the paediatric group changed much more during childhood than in adulthood, with a threefold to fourfold greater rate of DNA methylation changes in children versus adults[23]. These results suggest that some of the key methylation changes with age are programmed and take place during early life stages; by contrast, changes in methylation during adulthood may be the result of damage accumulation and the corresponding transcriptional responses[24]. Bioinformatic analyses in this paediatric population showed that the DNA methylation changes are enriched at genes with developmental and immune system functions, supporting the idea that these changes are probably part of the developmental programme[23]. Longitudinal studies of DNA methylation that assessed candidate genes and LINE1 repeats (which are long interspersed elements) in genetically identical twins reported that the variation in methylation over a 10-year period has a similar pattern in change to that observed in cross-sectional studies: there is an accumulation of independent stochastic DNA methylation changes over time[25].

Initially, there was a common belief that, as for gene expression studies, findings regarding DNA methylation in one tissue type would not translate to other tissues. However, age-associated differentially methylated regions in whole blood[26] have been replicated not only in specific haematopoietic cell types, but also in buccal cells. Another study also found that mean methylation levels and age–methylation correlations are well preserved between the brain and blood[21]. These studies support the view that age-associated DNA methylation changes are often shared among tissues within the same individual[25], although more and larger studies are needed for confirmation.

It should be noted that most studies carried out in the blood do not correct for blood cell counts, which introduces error. Nonetheless, the cross-tissue findings suggest that results may be robust. For example, a recent study applied a novel algorithm that integrates DNA methylation

with a protein interaction network to the context of cancer and ageing[27]; the aim was to identify specific pathways (that is, 'hot spots') associated with these two processes. This analysis revealed tissue-independent differentially methylated hot spots enriched for a stem cell differentiation pathway; the results were validated in independent data sets encompassing more than 1,000 samples in different tissue types and were robust to adjustment for blood-cell counts[27].

A key question is whether changes in the 'methylome' with age correspond to changes in the human transcriptome. This seems to be generally the case for the methylation sites examined by arrays, which mostly map to gene promoters; it has been reported that genes with age-associated expression profiles are more likely to have nearby age-associated methylation markers in studies using whole blood[28]. The relationship between methylation levels and transcription needs to be examined in other tissues to confirm the general validity of these findings.

Some DNA methylation changes are also associated with age-related phenotypes. In a study that investigated not only age but also age-related phenotypes such as telomere length in lymphocytes, blood pressure, lung function, grip strength, bone mineral density, and both maternal and paternal longevity, DNA methylation changes were strongly and independently correlated with age-related traits, supporting the idea that some of the changes in methylation status are related to biological ageing[29]. Epigenome-wide scans for methylation changes with chronological age identified hundreds of predominantly hypermethylated regions of which only one (at *TBX20*) was also associated with an age-related phenotype (namely, maternal longevity)[29]. Interestingly, *TBX20* encodes a transcription factor that is involved in cardiac development[29].

Metabolomics and ageing

The biochemistry of ageing is complex, and important changes occur in proteins, nucleic acids and lipids. Metabolomics explores such changes that are induced by treatments or changes that result from, or contribute to, a phenotype[30]. It aims to profile all low-molecular-mass metabolites that are present in biological samples such as serum or urine. Currently, analyses of metabolites can assess several hundreds of molecules, depending on the platform, but no single technology can measure the complete metabolome. Nuclear magnetic resonance (NMR) or mass spectrometry (MS) can be used for non-targeted metabolomics, which is suitable when the aim is to detect novel differences among samples, such as diseased versus healthy samples (see REF. 31 for a discussion of metabolomics technologies).

Some studies have now analysed metabolite changes with age. A study of 269 individuals using more than 200 metabolites reported significant correlations with age for 51 metabolites[32]. A study of 2,162 healthy individuals with a wide age range (32–81 years) using 131 metabolites from the Biocrates panel (which measures markers mostly related to lipid and carbohydrate metabolism) showed that metabolic profiles — especially profiles relating to incomplete mitochondrial fatty acid oxidation — are strongly correlated with age[33]. The broader Metabolon panel (containing 456 metabolites) has also been used for the characterization of metabolic profiles with age in a discovery sample of 6,055 twins carried out in the United Kingdom, and the key findings were replicated in 887 individuals from Germany[34]. This study identified a C-linked glycosylated tryptophan (C-glyTrp), the presence of which was highly correlated with age and ageing traits, such as lung function, bone mineral density and blood pressure. C-glyTrp was also associated with birthweight (which is a well-known developmental determinant of healthy ageing) and birthweight discordance between identical twins: its circulating levels were associated with methylation at the promoter of a regulator of translation elongation factor 2 (*WDR85*), providing a potential mechanism for the 'developmental origins of adult disease' hypothesis[35]. Using a lipidomic panel, a Dutch study[36] compared 1,526 middle-aged offspring of nonagenarians to 675 controls and found that 19 of 128 lipid species were significantly associated with familial longevity. These findings suggest that improved antioxidant capacity and more efficient β-oxidation function might be responsible for increased lifespan in humans[36].

Future directions and challenges

Metagenomics. There are several areas of omics studies for which there is growing interest in the field of ageing research. The human intestinal microbiota is composed of billions of microorganisms (the 'microbiome'), the collective genome of which is often referred to as the 'metagenome' (REF. 37). Because the microbiome influences host physiology, age-related differences in the gut microbiome composition and reduced microbiome diversity (which can be due to the changing environment of the elderly subject) may be related to the progression of diseases and frailty[38]. For example, a recent study found strong associations between microbiota composition (derived

Glossary

β-oxidation
The process of breaking down fatty acids to form acetyl-CoA. Occurs in mitochondria.

Biocrates
One of the metabolomics companies using a mass-spectrometry-based technology platform, mostly based on lipids.

Bisulphite sequencing
The treatment of DNA with bisulphite chemically converts unmethylated cytosines to uracil. As methylated cytosines are unaffected, the location of methylation can be identified by sequencing the bisulphite-treated DNA.

Differentially methylated regions
Genomic regions that exhibit significant differences in DNA methylation between sample groups.

Infinium BeadChip arrays
Manufactured by Illumina, these arrays allow the simultaneous testing of methylation levels at several thousands of CpG sites (methylation probes).

Metabolomics
The directed use of quantitative analytical methods for analysing the entire metabolic content of a cell or organism (that is, the metabolome) at a given time.

Metabolon
One of the metabolomics companies using a mass-spectrometry-based technology platform, which covers known and unknown metabolites.

Metagenomics
Describe the techniques that characterize the genomes of whole communities of organisms rather than individual species.

***N*-glycans**
Glycans are oligosaccharides linked to a protein. *N*-linked glycans are attached in the endoplasmic reticulum to the nitrogen in the side chain of asparagine in an Asn-X-Ser or Asn-X-Thr sequence, in which X is any amino acid except proline.

Progeria syndromes
Rare inherited diseases that cause rapid ageing and shortened lifespans, such as Hutchinson–Gilford progeria and Werner's syndrome.

from sequencing the 16S gene) and frailty, co-morbidity, nutritional status and markers of inflammation[39]. Indeed, the co-evolution of humans and bacteria makes it likely that the symbiotic relationship extends to the ageing process[37]. As this field progresses, it will become increasingly feasible to assess the role of the metagenome in the health status of the elderly, and also to assess its changes over time and its relationship to diet, medication and other environmental variables.

Proteomics. One area of long-awaited research is proteomics; indeed, some direct and indirect proteomic approaches show substantial promise for investigating ageing. For example, glycosylation is the only post-translational modification (PTM) that can produce significant structural changes to proteins[40], and the technology to assess glycosylation has recently become high throughput[41]. Emerging work has included the profiling of *N*-glycans on human serum glycoproteins (including immunoglobulins) in healthy individuals from different age groups, which revealed substantial changes with increasing age[42]. Importantly, levels of *N*-glycans also correlate with human longevity and one of the longevity-related glycans is also associated with cardiovascular disease[43]. As it becomes possible to assay other PTMs — such as citrullinations, crosslinks, isomerizations, nitrosylations, glucoronidations and phosphorylations — by high-throughput assays, further avenues may be explored.

Integration. One of the main challenges facing omics studies in the context of ageing is integrating the different types of data. Such integration should incorporate network analysis and annotation of the pathways involved, as well as interactions with key environmental factors — such as nutrition and other lifestyle factors — affecting the pathways. Such factors can alter the dynamic molecular omics measurements and have not yet been incorporated into the omics studies of ageing. Other obstacles include technological limitations, batch effects, differences between tissues and unreplicated false-positive results. All omics techniques involve genome-wide, or semi-genome-wide, approaches or extensive panels (for example, of metabolites or glycans) and hence there is a need for stringent guidelines for significance thresholds and a need for replicates to avoid reporting false positives. Furthermore, in order to assess which of the molecular markers have essential roles in ageing and are not merely a consequence of the ageing process, functional studies and longitudinal cohort studies (which can distinguish between age-related changes either taking place before the onset of, or as a consequence of, an age-related trait) will be crucial.

For some omics, such as glycomics, metabolomics and metagenomics, clear age correlations have been observed, but much data remain to be gathered and analysed. For transcriptomic studies, the current overall picture is that there are substantial changes with age but so far these have mainly been identified as tissue- and species-specific changes. In addition, changes seen in the transcriptome do not always reflect what is happening at the protein level. Some of the most substantial recent advances have come from DNA methylation studies, in which a large number of studies showed consistent patterns across tissues and strong age dependence, although comprehensive longitudinal data are needed. The studies reported so far demonstrate that omics technologies are increasingly important and are exciting tools in our bid to understand the complexities of ageing.

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Competing interests statement
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