EMBO *reports*

meeting report

Molecular basis of ageing

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The 94th Annual Boehringer Ingelheim Fonds International Titisee Conference was held at the Schwarzwald hotel in Titisee, Germany, from 11 to 15 April 2007. The conference was co-chaired by J. Hoeijmakers and J. Campisi, and was organized by H. Frolich.

Keywords: cancer; dietary restriction; longevity; oxidative stress; stem cells

EMBO *reports* advance online publication 7 September 2007; doi:10.1038/sj.embor.7401066

Introduction

The 94th Annual Boehringer Ingelheim Fonds International Titisee Conference brought scientists from around the world together to discuss recent progress in studies of the basic biology of ageing (biogerontology). The field of biogerontology has seen a marked growth in scientific and popular interest over the past few years, leading to an influx of new investigators working on diverse aspects of cellular and organismal ageing. This diversity was well represented at the conference, where topics included the molecular causes of ageing, cell senescence and apoptosis, stem cells, cancer, the genetics of longevity and anti-ageing interventions, among others. Although the range of topics was broad, the meeting gave rise to potential models through which this diversity might coalesce into a more comprehensive understanding of how and why we age.

One theme underlying much of the discussion at the conference was which approaches—both current and future—might facilitate the transition from basic research to therapeutic treatments for age-associated diseases. The potential benefits of successfully accomplishing such a transition are considerable. For example, it has been estimated that a single intervention to slow ageing in humans—such as dietary restriction (DR), which is now routine in mice—would increase life expectancy in the United States to a greater extent than simultaneously curing cancer, cardiovascular disease and diabetes (Miller, 2002; Olshansky *et al*, 1990). The molecular basis of ageing was therefore a timely and exciting topic for the 2007 Boehringer Ingelheim Fonds International Titisee Conference.

Molecular causes of ageing

At a fundamental level, biological ageing can be thought of as a progressive decline in the function of the cells of an organism, ultimately resulting in senescence. Despite much study, a clear understanding of the molecular causes of ageing has remained elusive. Although it is generally recognized that ageing is associated with the accumulation of cellular damage—for example, owing to the production of oxidative radicals (Harman, 1956)—there remains a lack of consensus in the field about the extent to which the accumulation of different types of damage drives the ageing process. Therefore, major themes of the conference were the potential molecular causes of ageing and the roles that many different factors might have in contributing to cell loss and tissue decline with age.

The conference opened with the keynote address by G. Martin (Seattle, WA, USA), who gave an overview of the pathobiology of ageing, with an emphasis on the classes of gene action that have escaped the force of natural selection. He concluded that, in contrast to the crucial role of the constitutional genome in the modulation of inter-specific variation in rates of ageing, stochastic events (possibly epigenetic in origin) are likely to be the main modulators of intra-specific variation in rates and patterns of ageing. D. Sinclair (Boston, MA, USA) also touched on this idea by proposing that DNA damage might be a cause of the stochastic loss of gene regulation with age due to global changes in histone acetylation.

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Submitted 3 July 2007; accepted 2 August 2007; published online 7 September 2007

Telomere shortening

The telomere hypothesis of ageing has been an important human model for nearly 20 years (Harley *et al*, 1992). This hypothesis posits that many age-associated phenotypes are caused by cellular senescence in response to one or more crucially shortened telomeres. In most human cells, telomere length is reduced with each cell division because the enzyme responsible for replacing the telomere ends, telomerase, is unexpressed or expressed at low levels. Replicative senescence of human cells in culture can be rescued by the expression of telomerase, demonstrating that it is sufficient to prevent cell senescence *in vitro* (Bodnar *et al*, 1998). The extent to which telomere shortening is relevant to cellular senescence and ageing *in vivo*, however, remains unknown.

J. Shay (Dallas, TX, USA) expressed optimism that telomerase inhibitors will be potent anti-cancer therapies. Shay discussed two classes of therapeutic telomerase inhibitor that are under development. The first is a synthetic telomerase peptide vaccine that is designed to elicit an immune response against a telomerase peptide present on the surface of cancerous cells. The second is an oligonucleotide complementary to the RNA component of telomerase that acts as a direct enzyme inhibitor. L. Rudolph (Hannover, Germany) discussed the possibility that telomere attrition in stem-cell populations is a key feature of ageing tissues. He proposed that transient activation of telomerase might be sufficient to replenish stem-cell telomeres without promoting tumorigenesis. Rudolph also showed data from experiments in telomerase-deficient mice (Rudolph *et al*, 1999), indicating that cell senescence and apoptosis in cells with crucially short telomeres can be prevented by interfering with a DNA-damage-response pathway.

DNA damage and oxidative stress

The accumulation of macromolecular damage has long been thought to underlie ageing at a fundamental level. One potentially important type of age-associated damage might be mutagenic damage to nuclear or mitochondrial DNA. J. Vijg (Novato, CA, USA) described a system for quantifying the frequency of different types of nuclear DNA mutation *in vivo* in flies and mice. Vijg reported that mutation rates were elevated in the liver in one short-lived mouse model and were reduced in the kidneys in two long-lived models: Ames dwarf mice and DR mice. V. Bohr (Baltimore, MD, USA) argued that mitochondrial base-excision repair has an important role in protecting against oxidative damage to mitochondrial DNA and noted that DR induces this type of repair.

Meeting co-chair J. Hoeijmakers (Rotterdam, The Netherlands) described progeroid and cancer phenotypes observed in several lines of knockout mice that are deficient for nucleotide-excision repair. Many human diseases, some with characteristics suggestive of premature ageing—such as Cockayne syndrome and trichothiodystrophy—are caused by these types of mutation (Andressoo *et al*, 2006). On the basis of gene-expression analysis in DNA-repair-deficient mice, Hoeijmakers speculated that nuclear DNA damage might invoke a longevity response by influencing insulin-like growth factor 1 (IGF1) and growth hormone (GH) signalling, which are known to have important roles in determining longevity from studies in model organisms.

Cancer and senescence

Several talks at the meeting underscored a growing recognition that cancer and ageing might be two sides of the same coin. Cancer is held in check by tumour-suppressing mechanisms that limit unregulated cell division early in life. However, these same anti-cancer pathways also lead to cellular senescence and apoptosis, which might ultimately drive age-related decline in tissue and organ function. Too little tumour-suppressing activity leads to an increased risk of cancer, whereas too much tumour-suppressing activity results in cell depletion and phenotypes consistent with premature ageing.

Much of the discussion at the meeting on this topic was centred on the p53 pathway and its role in age-associated disease. Meeting co-chair J. Campisi (Berkeley, CA, USA) discussed the importance of p53 in promoting senescence to prevent cancer. A large body of work from the Campisi laboratory and others has described the detrimental effects that factors secreted by senescent cells have on the surrounding tissues, which, paradoxically, might contribute to elevated cancer incidence and chronic inflammation with age (Campisi, 2005). Campisi reported that, as well as promoting cell senescence, p53 is crucial for keeping the secretion of these factors by senescent cells in check. Therefore, p53 apparently functions as a tumour suppressor both cell-autonomously and non-autonomously.

Ageing phenotypes in mice with altered p53 activity were also discussed at the meeting. M. Perry (Bethesda, MD, USA) described mice with a hypomorphic allele of the p53 inhibitor mouse double minute 2 (Mdm2). Too little Mdm2 is lethal, but reduced Mdm2 in transgenic mice leads to enhanced p53 activity, increased apoptosis and decreased cancer formation in at least one cancer-prone model. Interestingly, although cancer incidence is reduced, lifespan is unchanged (Mendrysa *et al*, 2006). H. Scrable (Charlottesville, VA, USA) described her work with mice that lack the primary p53 isoform but are still able to make an alternative isoform, p44 (Maier *et al*, 2004). Although these mice do not get cancer, they do seem to undergo accelerated ageing. She also described data indicating a role for p44 in the interaction of p53 with insulin/IGF1 signalling (IIS), and proposed that it might have a function in determining the ageing rate much earlier than had previously been thought—perhaps as early as embryogenesis.

Sinclair presented data indicating that increased expression of the silent information regulator 2 homologue 1 (SirT1) protein deacetylase confers protection against colon cancer in mice. SirT1 has been previously reported to modulate p53 activity (Luo *et al*, 2001; Vaziri *et al*, 2001) and has been proposed to mediate some aspects of DR (Guarente & Picard, 2005; Kaeberlein & Powers, 2007; Longo & Kennedy, 2006). Sinclair also mentioned ongoing studies to determine whether mice overexpressing SirT1 are long-lived—a topic of great interest to the field.

Depletion of stem cells

Several talks at the meeting emphasized a growing recognition of the importance of stem cells in ageing. One hypothesis is that stem-cell depletion in mitotically active tissues leads to many of the phenotypes associated with ageing. This hypothesis is attractive because it provides a potential synthesis explaining how all of the proposed causes of age-associated cell loss (DNA damage, telomere shortening, mitochondrial dysfunction and so on) could converge to lead to widespread stem-cell depletion as an organism ages. An important prediction of this hypothesis is that stem-cell abundance or proliferative potential decreases with age. L. Jones (La Jolla, CA, USA) provided experimental evidence for such depletion, showing that germline stem cells are lost with age in the fruit fly (Fig 1).

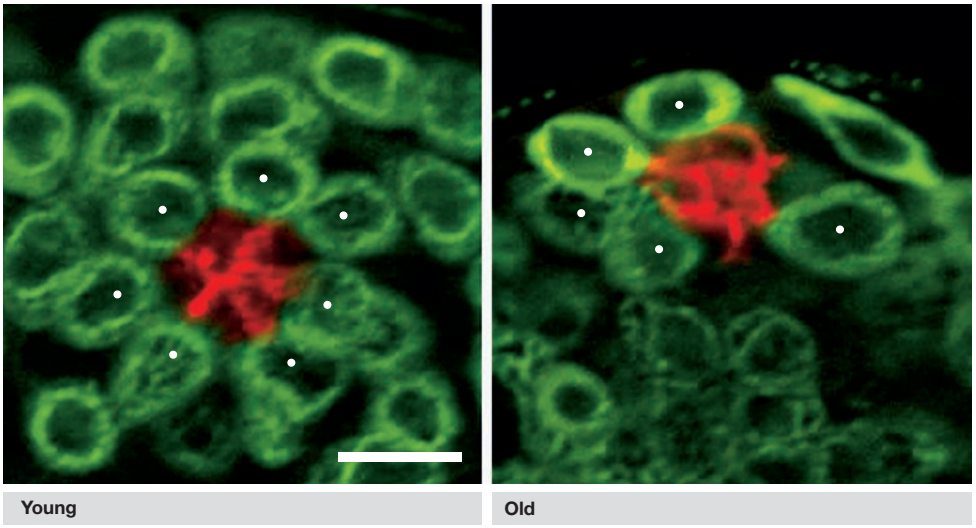

Fig 1 | Age-related loss of germline stem cells. Immunostaining for the germ-cell-specific RNA helicase Vasa (green) and the cell-surface protein fasciclin III (red) to mark the hub in young (1-day-old) and old (50-day-old) flies. Germline stem cells reside at the tip of the testis surrounding and in contact with the hub. Each germline stem cell is indicated by a white dot. Image courtesy of L. Jones.

C. López-Otin (Oviedo, Spain) presented data indicating a potential link between stem-cell defects and the human progeroid disease, Hutchinson–Gilford progeria syndrome (HGPS). HGPS is caused by defective splicing of the lamin A/C gene, which results in the accumulation of unprocessed lamin A (De Sandre-Giovannoli *et al*, 2003; Eriksson *et al*, 2003). Mice that lack the zinc metallopeptidase STE24 homologue (*Zmpste24*) gene, which codes for a protease that cleaves lamin A, similarly accumulate an unprocessed form of lamin A and show features of premature ageing (Pendas *et al*, 2002). These mice also had elevated p53 activity, accumulated quiescent stem cells and reduced stem-cell proliferation. López-Otin suggested that stem-cell therapy might prove useful for HGPS patients in the future.

Interventions that increase longevity

One of the great promises of biogerontology is the development of therapies to combat age-associated diseases. Interventions that slow ageing are likely to delay the onset of many important diseases, including cancer, diabetes, cardiovascular disease and neurodegenerative diseases. Indeed, in rodents, DR seems to have precisely this effect (Masoro, 2005; Weindruch & Walford, 1988). Several talks at the meeting focused on interventions that increase lifespan in model organisms and the potential to translate these discoveries into treatments for humans.

Dietary restriction

Although new models of enhanced longevity in mammals continue to be described, it was clear that DR remains the gold standard against which these models are compared. Known to increase lifespan in yeast, worms, flies and rodents, DR is the best studied anti-ageing intervention. Much discussion at the meeting centred on the pathways that are thought to mediate DR and the development of DR mimetics—chemicals designed to target these pathways to provide the health and longevity benefits of DR, without requiring reduced food consumption.

S. Spindler (Riverside, CA, USA) described an approach for identifying DR mimetics that involves gene-expression profiling. He mentioned published data (Dhahbi *et al*, 2005) showing that metformin, which is an anti-diabetic compound already known to increase lifespan in mice (Dilman & Anisimov, 1980), recapitulates most of the gene-expression changes associated with DR. One target of metformin is adenosine-monophosphate-activated protein kinase (AMPK), which is known to regulate metabolic and mitochondrial function in response to nutrients (Zhou *et al*, 2001). Interestingly, AMPK is also activated by resveratrol (Dasgupta & Milbrandt, 2007; Zang *et al*, 2006), which is a putative DR mimetic that has recently gained much attention for its reported ability to improve the health and median survival of mice fed a high-fat diet (Baur *et al*, 2006; Lagouge *et al*, 2006).

M. Kaeberlein (Seattle, WA, USA) and T. Johnson (Boulder, CO, USA) both presented data from experiments in the nematode *Caenorhabditis elegans* indicating that DR increases survival and reduces mortality even when initiated late in life. These observations are similar to the effect of DR in fruit flies (Mair *et al*, 2003). Spindler also discussed published data in mice indicating that DR initiated late in adulthood rapidly reduced mortality, and caused a shift in gene expression to a pattern similar to that seen in mice placed on a DR diet early in life (Dhahbi *et al*, 2004). Therefore, a consensus seems to be emerging that, at least in model organisms, DR initiated later in life still has beneficial results for health and longevity. Although it remains to be determined to what extent DR slows ageing in humans, these studies provide hope that DR mimetics will be effective against age-associated disease in middle-aged adults.

Growth hormone and insulin/IGF1 signalling

GH supplementation has received notoriety as a potential anti-ageing treatment, but so far has not been proven to be effective in this regard (Perls, 2004). J. Kopchick (Athens, OH, USA) made the case that, although GH supplementation is therapeutic for individuals suffering

from GH deficiency, in healthy adults it might have adverse consequences, including an increased risk of cancer. Kopchick and A. Bartke (Springfield, IL, USA) both noted that in several rodent models, including GH-receptor-knockout mice, Ames dwarf mice and Snell dwarf mice (Brown-Borg *et al*, 1996; Coschigano *et al*, 2000; Flurkey *et al*, 2001), reduced GH signalling, rather than elevated GH activity, is correlated with increased longevity.

Although reduced GH signalling correlates with increased lifespan in mice, simply inhibiting GH activity might not be sufficient to slow ageing. Kopchick reported that mice treated with a peptide GH antagonist are not long-lived. This might be owing to effects specific to the GH agonist used in these studies or it could indicate that other hormonal factors in addition to GH are crucial for the enhanced longevity of the dwarf mice. As the detailed mechanisms accounting for lifespan extension in GH-receptor-knockout and dwarf animals are uncovered, more-targeted therapies to alter GH activity might prove useful against a wide range of age-associated diseases.

In addition to reduced levels of GH, one feature that long-lived dwarf mice and mice subjected to DR have in common is reduced insulin and IGF1 levels (Bartke, 2005). Reduced IIS is known to increase the lifespan of worms and flies, which points to an evolutionarily conserved mechanism of action (Longo & Finch, 2003). Surprisingly, genetic evidence has indicated that IIS and DR act in parallel genetic pathways, based on additive increases in lifespan observed when DR is imposed on *C. elegans* mutants with reduced IIS (Houthoofd *et al*, 2003; Kaeberlein *et al*, 2006; Lakowski & Hekimi, 1998; Lee *et al*, 2006) or Ames dwarf mice (Bartke *et al*, 2001). Bartke discussed the relationship between reduced GH or IIS signalling and DR, and concluded that they are related, but not identical. This idea fits with data from R. Miller (Ann Arbor, MI, USA), which showed that fibroblasts from Ames dwarf, Snell dwarf or GH-receptor-knockout mice are resistant to a range of stresses in culture, but that a similar phenotype is not observed in fibroblasts from DR animals (Harper *et al*, 2006).

Bartke presented data consistent with the idea that insulin sensitivity is an important predictor of longevity in rodents. Although GH-receptor-knockout mice and Ames dwarf mice respond differently to DR with respect to longevity, in each case a strong correlation between insulin sensitivity and lifespan was observed. R. Westendorp (Leiden, The Netherlands) described a similar correlation in long-lived humans and their offspring, and suggested that human longevity might be associated with more-efficient glucose handling. Bartke also presented evidence that decreased GH or IIS could promote longevity in part by reducing signalling through the nutrient-responsive target of rapamycin (TOR) kinase pathway, which is known to increase lifespan in yeast, worms and flies (Jia *et al*, 2004; Kaeberlein *et al*, 2005; Kapahi *et al*, 2004; Powers *et al*, 2006; Vellai *et al*, 2003). TOR signalling has been proposed to mediate lifespan extension from DR in simple eukaryotes (Kapahi & Zid, 2004), and might provide an important molecular link between GH, IIS and DR in mammals.

Conclusion

The 94th Annual Boehringer Ingelheim Fonds International Titisee Conference on the molecular basis of ageing demonstrated both the complexity and the potential rewards of biogerontology. Although much remains to be discovered, patterns and connections are emerging, and biogerontologists are generally optimistic that effective interventions targeting age-associated disease are on the horizon. Indeed, some of the studies discussed in Titisee are already being translated into potential therapies for specific age-associated diseases.

Although efficacy has yet to be demonstrated for any 'anti-ageing' intervention, it is likely that the process of moving from basic biogerontology to therapeutic applications will accelerate. It will be interesting to follow the stories told at Titisee and to see which make this transition. Will stem-cell therapies be useful for targeting age-associated diseases? Are DR mimetics feasible and will they be beneficial to humans? Can telomerase activity or GH signalling be effectively modulated in humans to influence ageing and cancer? These questions and many others of importance to the field will probably be answered in the next few years. We therefore look towards the future of biogerontological research, and the next Boehringer Ingelheim Fonds Conference on the molecular mechanisms of ageing, with anticipation and enthusiasm.

ACKNOWLEDGEMENTS

The meeting was sponsored by the Boehringer Ingelheim Fonds Foundation for Basic Research in Medicine. I thank G. Martin for helpful discussions and comments on this meeting report. Many thanks to J. Hoeijmakers, J. Campisi and H. Frolich for their efforts organizing the conference, and to all the participants for their outstanding presentations and discussions. I apologize to those participants who could not be included in this review because of space constraints.

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