Ageing Research Reviews 12 (2013) 310–315

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Nucleic acid delivery: Roles in biogerontological interventions

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ARTICLE INFO

Article history:
Received 26 June 2012
Received in revised form 29 August 2012
Accepted 30 August 2012
Available online 7 September 2012

Keywords:
Biogerontology
Intervention development
Lifespan
Longevity
Nucleic acid delivery

ABSTRACT

Prolongation of longevity is a history-long desire of humans. Driven by the genetic contribution to longevity and the remarkable plasticity of healthy lifespan as demonstrated in animal models, arduous efforts have been directed to aging and longevity research over the years. Today, our understanding of lifespan determination is much greater than it was in the past, but administrable interventions for longevity enhancement are still virtually absent. The aim of this article is to highlight the technical gap between basic biogerontological research and intervention development, and to explore the importance of nucleic acid (NA) delivery technologies in bridging the gap. It is hoped that this article can engender more awareness of the roles of NA delivery technologies in biogerontological interventions, particularly NA therapy.

1. Introduction

Prolongation of longevity is a long-held desire of mankind. As early as the Middle Ages, European alchemists were experimenting with chemicals in an attempt to create life (Lai and Chan, 2010). Cravings for longevity also existed in ancient China when *Ying Zheng*, also named *Qin Shi Huang*, sent Taoists overseas to search for an elixir of immortality. With intensive genetic studies on lifespan determination over the years (Cutler, 2005; de Magalhaes, 2011; Evans et al., 2011; Tranah, 2011), our understanding of aging and longevity has evolved tremendously, repositioning the notion of lifespan extension from simply a fantasy in the past to a viable reality at present.

For centuries, human lifespan has been considerably extended. As projected by Christensen et al. (2009), babies born since 2000 in countries with long life expectancy (such as Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States) may live to an age of 100 if human life expectancy continues to improve at the same pace as it had over the past two centuries. Despite the encouraging trend, till now human life expectancy has been improved mainly as a result of more effective geriatric care and better living conditions, involvement of interventive biogerontology is infinitesimal. The latter can be evidenced by the virtual absence of administrable interventions for lifespan prolongation at present, and such absence may be partly due to the deep-seated notion circulating in today's scientific societies that lifespan is just a natural trait and any quest to intervene with it is unnecessary and bound to fail. While such a notion, and the consequences inexorably followed [including the unjustified reluctance among scientists to go anywhere beyond basic aging research (de Grey et al., 2002), and the hesitancy of funding agencies to invest on development of interventions for lifespan prolongation (de Grey, 2010)], have profoundly obstructed advances in interventive biogerontology, the technical gap between basic biogerontological research and intervention development is also worth noting. The main purpose of this article is to focus on the latter by exploring the importance of nucleic acid (NA) delivery technologies to biogerontological interventions, particularly NA therapy.

2. From research to hypothetical interventions

Lifespan is a trait determined not only by environmental factors, but also by genetic elements. The latter was suggested by Herskind et al. (1996), who analyzed 2872 pairs of non-emigrant like-sex twins and found that the heritabilities of longevity for males and females are around 0.26 and 0.23, respectively. The genetic contribution to longevity was further corroborated by some recent studies, which examined the concordance of longevity in monozygous and dizygous twins and estimated that 25–30% of lifespan variation is contributed by genetic factors (Gudmundsson et al., 2000; Skytthe et al., 2003; Hjelmborg et al., 2006; Slagboom et al., 2011). In light of this, and along with the recognition of major pathways of lifespan regulation [including the target of rapamycin pathway (Sheaffer et al., 2008) and the insulin/insulin-like growth factor-1 (IGF-1) signaling pathway (Papaconstantinou, 2009)], a vigorous search of molecular determinants of lifespan and biological aging has been stimulated since the 1980s. One of the

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http://dx.doi.org/10.1016/j.arr.2012.08.003

first gene mutants being demonstrated to increase lifespan was *age-1* (Friedman and Johnson, 1988). The gene was later found to encode a homologue of mammalian phosphatidylinositol-3-OH kinase catalytic subunits, and is germane to non-dauer development and normal senescence (Morris et al., 1996). Other examples of longevity-related genes include *AGTR1*, *sir-2.1*, *hcf-1*, *smk-1*, and *daf-16* (Wolff et al., 2006; Rizki et al., 2011; Benigni et al., 2012). Some of these genes have been extensively reviewed in the literature (Dali-Youcef et al., 2007; Landis and Murphy, 2010; Satoh et al., 2011).

In recent years, exploration of longevity-associated genes has been intensified by the escalating computational power. With advances in gene expression profiling, genome-wide expression profiles of different tissues [including brain (Hong et al., 2008), skeletal muscles (Zahn et al., 2006) and kidney (Rodwell et al., 2004)] have already been reported on individuals of various ages. This provides valuable data to facilitate generation of biological hypotheses regarding the transcriptional regulation of aging for future experimental validation. More currently, genome-wide analysis has also been conducted by Seong and coworkers on low-dose irradiated male *Drosophila melanogaster*, which exhibited extended longevity (Seong et al., 2011). By measuring the gene expression patterns, a set of genes underlying ionizing radiation-induced lifespan extension were recognized. Examples of these genes include cytochrome-related genes (*Cyp1*, *Cyp4d21*, *Cyp4p3*, *Cyp6a9*, *Cyp6g1*, and *Cyp318a1*), genes relating to protein turnover and ubiquitination pathways (*e.g. CG2924*, *CG7220*, *crl*, *neur*, *Roc1b*, *Ubc84D* and *Ubc-E2H*), and genes responding to oxidative stress (*e.g. GstS1*, *Jon65Ai*, *Jon65Aiv*, *Jon66Ci*, *Jon99Ci*, *Jon99Cii*, *mmd*, *Trxr-1*, and *Trxr-2*). These candidate genes are worth further verification as possible targets for lifespan prolongation.

Lately, the advent of single nucleotide polymorphism (SNP) genotyping technologies has opened the prospect of genome-wide association studies (GWAS). GWAS are a prodigious means to examine hundreds of thousands of SNPs across the entire genome, and to identify new genetic signatures that are associated with the phenotype of interest (Kronenberg, 2008). Though the problems of poor reproducibility and false positive findings are some issues that have yet to be completely resolved, compared to candidate-gene studies, GWAS need no prior assumption regarding gene functions. This makes GWAS advantageous for mapping genetic variants (even those whose mechanistic roles are currently unknown) underlying the examined biological process. By analyzing the GWAS data of 403 unrelated nonagenarians from long-lived sibships and 1670 younger population controls, Deelen et al. (2011) discovered that *POT1* plays a major role in associating the telomere maintenance pathway with human longevity. They also found that the association of the insulin/IGF-1 signaling pathway with longevity was determined largely by the following genes: *AKT3*, *AKT1*, *FOXO4*, *IGF2*, *INS*, *PIK3CA*, *SGK*, *SGK2*, *YWHAG* and *POT1*. Their study has illuminated how genetic variations in genes involved in these two pathways contribute to lifespan determination. In fact, though GWAS have been used more commonly in studies of age-related diseases (Kronenberg, 2008) (such as cancers, diabetes mellitus and atherosclerosis) rather than of longevity *per se*, it is expected that research on this track can deepen our understanding of the genetics of longevity in the future.

In order to enhance longevity, one of the key issues to be confronted is aging. Hitherto, three major approaches have been proposed to resist the aging process at different levels (Fig. 1). As prevention is more cost-effective and humane than disease diagnosis and cure (Weinstein, 1990), compared to the geriatric means which alleviates geriatric symptoms only when they cause diseases, the gerontological and engineering approaches are more proactive in nature and hence more desirable. The basic idea of the gerontological approach is to manipulate the fundamental metabolic pathways so as to resist aging and enhance longevity. The technical possibility of this approach has been established by the cumulative biogerontological endeavors in identification of candidate genes potentially linked with aging and longevity determination (Swindell, 2007; Kim et al., 2012). However, empirical verification of the anti-aging or longevity-enhancing effects of a gene or an intervention necessitates years of dedication in mouse (Kaeberlein, 2007), and is almost nonviable in humans whose low birth rate and long lifespan make the experimental time required unaffordable. For this, various simpler eukaryotes (such as *Caenorhabditis elegans*, *Drosophila melanogaster* and *Saccharomyces cerevisiae*) have been exploited as alternative models, and in these models the possibility of transgenic manipulation for lifespan extension has been corroborated. For instance, by overexpression of the *D-GADD45*

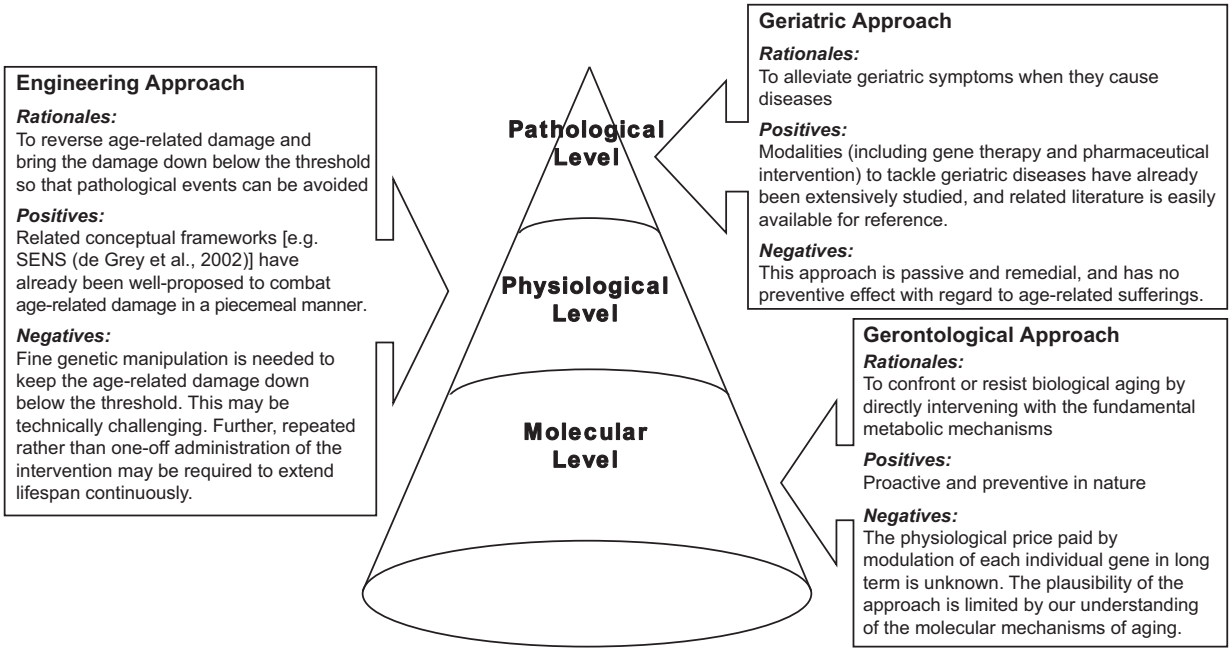

Fig. 1. Three major approaches targeting different levels of the aging process.