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Review

The zebrafish as a gerontology model in nervous system aging, disease, and repair

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ABSTRACT

Considering the increasing number of elderly in the world's population today, developing effective treatments for age-related pathologies is one of the biggest challenges in modern medical research. Age-related neurodegeneration, in particular, significantly impacts important sensory, motor, and cognitive functions, seriously constraining life quality of many patients. Although our understanding of the causal mechanisms of aging has greatly improved in recent years, animal model systems still have much to tell us about this complex process. Zebrafish (*Danio rerio*) have gained enormous popularity for this research topic over the past decade, since their life span is relatively short but, like humans, they are still subject to gradual aging. In addition, the extensive characterization of its well-conserved molecular and cellular physiology makes the zebrafish an excellent model to unravel the underlying mechanisms of aging, disease, and repair. This review provides a comprehensive overview of the progress made in zebrafish gerontology, with special emphasis on nervous system aging. We review the evidence that classic hallmarks of aging can also be recognized within this small vertebrate, both at the molecular and cellular level. Moreover, we illustrate the high level of similarity with age-associated human pathologies through a survey of the functional deficits that arise as zebrafish age.

Contents

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1. Introduction

1.1. Age-related deterioration of the CNS

Aging is the ultimate embodiment of numerous alterations of intrinsic and extrinsic cell components. The energy-demanding neurons of the central nervous system (CNS) are particularly vulnerable to aging, since the accumulation of damaged proteins, lipids, and nucleic acids greatly impairs their protein synthesis and vitality (Mattson and Magnus, 2006). Moreover, changes in their cellular environment, including the phenotype of e.g. astrocytes and oligodendrocytes, can significantly influence the fate of vulnerable neurons (Salminen et al., 2011). Indeed, both a reduction of synaptic efficacy and neuronal cell loss are evident in the senescent CNS (Rando, 2006; Yeoman et al., 2012). This inevitably affects sensory, motor, and cognitive functions and is strongly intertwined with the development of age-related pathologies (Brighina et al., 2010; Kovacs et al., 2014; Vardy, 2015). Intensive research efforts therefore focus on the attenuation of aging processes and/or the resolution of associated neurodegenerative diseases, which should lead to greatly improved medical care for an aging world population.

Despite the rate at which this research is progressing, and its clear importance for human health, a complete understanding of the molecular and physiological mechanisms of CNS senescence is still lacking. This is because the process of aging is almost certainly pleiotropic in nature, and the mechanisms vary widely across vertebrate species (Sasaki and Kishi, 2013; Yeoman et al., 2012). Nevertheless, with an appropriate synthesis this diversity of senescence-related pathways should yet prove to be more of a help than a hindrance, as different animal models each contribute towards our understanding of different parts of the aging mechanism; whether they be the role of specific genes, molecular mechanisms, or the complex intercellular interactions involved in aging. Precise genetic or pharmacological manipulations within different animal model systems indeed allow the identification of aging agents within different physiological systems and/or functions. It therefore seems likely that only a combination of data collected in different models will help to decipher the principal factors that underlie aging.

1.2. The zebrafish: a continuum through development, maturation, and aging

Several model organisms, from microscopically small invertebrates to primates, have been the focus of investigation for the mechanisms of aging (López-Otín et al., 2013). Among these different species the rate of physiological decline varies, and the process of senescence can generally be classified from rapid to gradual to negligible. Invertebrates commonly demonstrate a swift development, short life span, and rapid aging. Whilst they still offer great insights into underlying cellular and molecular mechanisms, they do not experience the slow deterioration that characterizes mammalian aging. As such, worms and insects are unlikely to die from typical chronic age-related human pathologies, such as cancer and stroke (Sasaki and Kishi, 2013). The majority of vertebrates, on the other hand, display gradual senescence, often associated with a long maximum lifespan. Detailed gerontology research in models of baboons (30 years) (Herbig et al., 2006) and birds (seven years and longer) (Holmes et al., 2001) are thus often exhausting, which is why mice (living for two to three years) are mostly the model of choice (Vanhooren and Libert, 2013).

Fish have been much overlooked in gerontology research and have only partially been exploited to shed light on the fundamental biological process of aging. Some teleost species have a relatively short median life span of only three and a half years, while still allowing the study of aging mechanisms as they gradually unfold, e.g. medaka (*Orizias latipes*) (Ding et al., 2010; Gopalakrishnan et al., 2013) and zebrafish (*Danio rerio*) (Kishi, 2004; Kishi et al., 2003). Although they live slightly longer than rodents, they share the feasibility of large-scale mutational analysis with invertebrate models (Gerhard, 2003).

In this context the zebrafish, in particular, has the potential to be of great value in gerontology research, given the wealth of developmental and genetic studies that have already driven an extensive characterization of basic zebrafish biology and relevant experimental techniques. This small vertebrate possesses several unique features that offer many advantages to the field. One female produces several hundred transparent eggs each week, which develop *ex utero* into fully free-swimming larvae in only four to seven days (Gerhard, 2003; Kimmel et al., 1995). Young adulthood is reached by the age of three to five months and coincides with the onset of reproductive activity (Gerhard and Cheng, 2002). Thousands of fish can thus be quickly acquired and easily maintained at very low cost. Moreover, most of the genome is sequenced and has proven to show high similarity to humans, with orthologs of many human genes (Barbazuk et al., 2000; Howe et al., 2013; Woods et al., 2000). A complex mammalian-like developmental gene program gives rise to an integrated nervous system, for which all the major brain regions have been mapped (Key and Devine, 2003; Rupp et al., 1996; Wullimann and Mueller, 2004), and which confers these fish with advanced cognitive functions and social behavior (Oliveira, 2013; Saverino and Gerlai, 2008). In addition, the wide availability of zebrafish-specific experimental procedures (gain- and loss-of-function approaches, *in vivo* imaging techniques) and resources (clones, antibodies, cell lines, reporter fish lines) would further support increased efforts into aging research in this species (Gerhard and Cheng, 2002).

Senescence has long been considered negligible in zebrafish, because they experience an indeterminate growth and possess a highly robust regenerative capacity. However, their growth rate seriously diminishes with age, they are reported to show a senescent morphology, and are subject to age-related morbidity and mortality (Gerhard et al., 2002; Tsai et al., 2007). Indeed, it was only recently established that zebrafish - like most vertebrates - are subject to gradual aging, and they are now increasingly valued as a model for gerontology (Gerhard and Cheng, 2002; Kishi, 2011). Continuous efforts over the past decade have started to elucidate aging pathways within the zebrafish, illustrating many parallels with other vertebrate species. They display the same typical markers (e.g. increased DNA damage (Shimoda et al., 2014) and elevated β-galactosidase expression (Kishi et al., 2003)) and exhibit senescent phenotypes which often resemble age-related pathologies known in humans (e.g. cognitive decline (Yu et al., 2006) and osteoarthritis (Hayes et al., 2013)).

Although a vast amount of information remains to be explored, the major advances in zebrafish gerontology further described in this review highlight that these and future comparative studies will make important contributions to our understanding of aging,

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