Seminars in Cell & Developmental Biology 70 (2017) 108–121

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Secrets from immortal worms: What can we learn about biological ageing from the planarian model system?

Sounak Sahu, Anish Dattani, A. Aziz Aboobaker*

Department of Zoology, South Parks Road, University of Oxford, Oxford OX1 3PS, UK

ARTICLE INFO

Article history:
Received 19 July 2017
Received in revised form 7 August 2017
Accepted 9 August 2017
Available online 15 August 2017

Keywords:
Stem cells
Neoblasts
Self-renewal
Genome stability
Regeneration
Tumour suppressor

ABSTRACT

Understanding how some animals are immortal and avoid the ageing process is important. We currently know very little about how they achieve this. Research with genetic model systems has revealed the existence of conserved genetic pathways and molecular processes that affect longevity. Most of these established model organisms have relatively short lifespans. Here we consider the use of planarians, with an immortal life-history that is able to entirely avoid the ageing process. These animals are capable of profound feats of regeneration fueled by a population of adult stem cells called neoblasts. These cells are capable of indefinite self-renewal that has underpinned the evolution of animals that reproduce only by fission, having disposed of the germline, and must therefore be somatically immortal and avoid the ageing process. How they do this is only now starting to be understood. Here we suggest that the evidence so far supports the hypothesis that the lack of ageing is an emergent property of both being highly regenerative and the evolution of highly effective mechanisms for ensuring genome stability in the neoblast stem cell population. The details of these mechanisms could prove to be very informative in understanding how the causes of ageing can be avoided, slowed or even reversed.

Contents

Abbreviations: NB, Neoblast; ROS, Reactive oxygen species; TSG, Tumour suppressor gene; PIWI, P-element-induced wimpy testis; piRNA, Piwi interacting RNAs; TEs, Transposable Elements; GSC, Germline Stem Cell; IR, Ionising Radiation; Gy, Gray; DDR, DNA damage response.

* Corresponding author.
E-mail address: aziz.aboobaker@zoo.ox.ac.uk (A.A. Aboobaker).

http://dx.doi.org/10.1016/j.semcdb.2017.08.028
1084-9521/

1. Introduction

Obtaining as complete an understanding of the biological ageing process as possible is important. A census of the Animal Kingdom will reveal that while the ageing process is assumed to be a characteristic of most taxa, it is not a pre-requisite of being a metazoan [1]. Some seem to avoid the physiological decline that characterises ageing altogether and, like Hydra [2,3] and planarians [4–8], are also capable of profound regenerative feats. Some of these regenerating animals can even be referred to as somatically immortal, based on the observation of a species life cycle that does not involve either sexual reproduction (and meiosis) or development from a zygote, but instead uses only regeneration for reproduction.

Animals traditionally used to study the mechanisms of ageing have relatively short life cycles and age rapidly, making the study of the ageing process convenient. These studies have led to an understanding of some of the genetic regulation underpinning ageing and the realisation that some aspects of the ageing process are conserved [9,10]. In contrast to this, the study of long-lived or immortal animals has lagged far behind, as these organisms were not amenable to classical genetic approaches, and therefore studying the underlying mechanisms as to why ageing is apparently absent was clearly problematic. However, advances in molecular genetics have now made these animals experimentally tractable [11].

Understanding how some animals have evolved to avoid the ageing process may provide novel ideas about how we can eventually alleviate the problems associated with ageing human populations, and the many age associated diseases, like cancer and dementia, that accompany this [12]. Here we focus on discussing planarian flatworms [7,8]. They have been formally studied as a research system for well over a century and early on were recognised as potentially immortal [13,14]. These animals are famous for their powers of regeneration, capable of regenerating all organs and tissues of the body from small starting fragments. This ability is fuelled by a population of pluripotent adult stem cells called neoblasts (NBs) capable of making all body tissues and undergoing indefinite self-renewal [15,16]. While current evidence supports the hypothesis that highly proliferative adult stem cells are a synapomorphy of the phylum Platyhelminthes [17,18], the extent of regenerative ability varies greatly across flatworms [19] and even within the Triclad planarians where head regeneration can be reactivated by genetic manipulation [20,21]. Planarians can reproduce sexually and in many cases, such as the major laboratory model species *Schmidtea mediteranea*, an asexual species that reproduces by exploiting regeneration has also evolved from the sexual state (Fig. 1A and B) [22]. In these scenarios reproduction has become entirely a collective function of the of the NB population, which as well as powering regeneration effectively take on the role of the germline [15,23]. For these asexual species to persist as a continuous adult population these somatic NBs must be collectively immortal and underpin ever-ongoing homeostatic maintenance of healthy adult tissues. Thus, both the endogenous and exogenous causes of ageing in most animals must be dealt with by this cell population. Given we now know many potential causes of ageing in animals we can ask: what are the cellular and molecular mechanisms behind the planarian life history traits that avoid ageing?

In this discussion we begin by briefly introducing planarian stem cell biology and homeostatic tissue maintenance processes that underpin the planarian immortal life history. We then consider some of the fundamental causes and consequences of ageing in mammals and humans that are relevant to the planarian life history and what is known about how planarians might avoid them. One major conclusion from this is that a combination of emergent features from being able to regenerate, NBs having properties normally associated with the immortal germline of animals and the increased activity of processes that promote genome stability, together underpin the immortal planarian life history.

2. An overview of planarian stem cells, tissue homeostasis and regeneration

2.1. The experimental accessibility of planarians and their NBs

While there is rich body of planarian research throughout the late nineteenth and twentieth century [14,16,24–26] it was the discovery of RNAi that catalysed a major rejuvenation in planarian research [27–30]. Over the last twenty years the ability to study gene function in planarians has allowed a growing research community to make in-roads into understanding the biology of these exciting animals [7,8,16]. Improvements in sequencing technology have also benefited planarian research leading to the sequencing of the *S. mediterranea* genome [31], many transcriptome studies [32–36], single cell expression profiling [37] and RNA sequencing [38–40] and genome-wide epigenetic studies [41–43]. The ability to accurately FACS sort NBs at different stages of the cell cycle and undifferentiated NB progeny from differentiated cells, based on nuclear to cytoplasmic ratios, has provided essential access to these cells to apply genome wide approaches [44,45]. These 'omic approaches, combined with an ever-growing list of cell and tissue markers and improved protocols of visualising gene expression in whole animals, provides a powerful set of tools for planarian researchers [46–49]. One notable absence is an approach for mis-expressing genes or exploiting genome editing tools, and this deficit needs urgent attention to improve the depth of mechanistic insight that can be achieved in this model system.

Due to these developments and some elegant experimental designs, we now understand some fundamental aspects of regeneration. One emerging theme so far being that well-known signalling pathways conserved in embryogenesis have conserved roles and interactions during regeneration [50–57]. Additionally, many similarities between NBs and mammalian embryonic and germline stem cells have been discovered [22,35,58]. This, along with other studies across the Animal Kingdom [59–61], has contributed to an appreciation of surprising levels of molecular conservation across animal stem cells and the mechanisms that underpin "stemness". One prominent view of ageing in mammals is that it can be viewed as a gradual accumulation of adult stem cell dysfunction [62–64], so this conservation of stem cell biology suggests that many discoveries made in planarians and other highly regenerative animals with stem cells will be directly relevant to our own ageing biology.

2.2. Planarian NBs are the driving force behind regeneration

Planarians are somewhat unusual in having adult stem cells that are collectively, and in at least some cases individually, pluripotent. Currently the consensus that NBs are those cells still within the cell cycle and that express transcripts considered to be pan-NB mark-