Ageing Research Reviews 21 (2015) 30–42

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

Ageing and inflammation – A central role for mitochondria in brain health and disease

Antonio Currais*

The Salk Institute for Biological Studies, 10010 N. Torrey Pines Rd, La Jolla, CA 92037, USA

ARTICLE INFO

Article history:
Received 9 November 2014
Received in revised form 29 January 2015
Accepted 2 February 2015
Available online 12 February 2015

Keywords:
Differentiation
Inflammation
Metabolism
Neurodegenerative diseases

ABSTRACT

To develop successful therapies that prevent or treat neurodegenerative diseases requires an understanding of the upstream events. Ageing is by far the greatest risk factor for most of these diseases, and to clarify their causes will require an understanding of the process of ageing itself. Starting with the question *Why do we age as individual organisms, but the line of pluripotent embryonic stem cells and germ cells carried by individuals and transmitted to descendants is immortal?* this review discusses how the process of cellular differentiation leads to the accumulation of biological imperfections with ageing, and how these imperfections may be the cause of chronic inflammatory responses to stress that undermine cellular function. Both differentiation and inflammation involve drastic metabolic changes associated with alterations in mitochondrial dynamics that shift the balance between aerobic glycolysis and oxidative phosphorylation. With ageing, mitochondrial dysfunction can be both the cause and consequence of inflammatory processes and elicit metabolic adaptations that might be either protective or become progressively detrimental. It is argued here that an understanding of the relationship between metabolism, differentiation and inflammation is essential to understand the pathological mechanisms governing brain health and disease during ageing.

Contents

* Tel.: +1 858 453 4100x1480; fax: +1 858 535 9062.
E-mail address: acurrais@salk.edu

http://dx.doi.org/10.1016/j.arr.2015.02.001
1568-1637/

1. Introduction

Ageing is the greatest risk factor for the majority of neurodegenerative diseases (Lin and Beal, 2006). Given the demographic challenge that ageing currently poses to societies and the lack of therapies that prevent or treat age-associated brain degeneration, neurodegenerative diseases are becoming the epicentre of concern for national health care systems. The need to develop successful therapies that tackle these diseases is turning the attention of scientists to the upstream events that cause the pathology. However, to identify those events requires an understanding of the process of ageing itself.

This review will discuss some of the current ideas on ageing and disease, starting with a single fundamental question: *Why do we age as individual organisms, but the line of pluripotent embryonic stem cells and germ cells carried by individuals and transmitted to descendants is immortal?* In other words, human embryonic stem cell and/or germ cell lines must possess certain characteristics that maintain immortality and protect themselves from ageing so that our species is propagated and thus perpetuated. Somehow, for most cells in complex multicellular organisms, these characteristics change or are lost when the process of cellular differentiation takes place.

Evolutionarily, the acquisition of mitochondria played a key energetic role in the establishment of biological complexity, expanding life from unicellular to multicellular (Lane and Martin, 2010). In fact, mitochondria are determinant to cellular differentiation by mediating numerous aspects of metabolism (Agathocleous and Harris, 2013; Folmes et al., 2012; Ito and Suda, 2014; Xu et al., 2013). Therefore, organismal complexity arises from the interaction and cooperation of individual cells with diverse and specialized functions that rely upon crucial metabolic adaptations. With age, changes in mitochondrial homeostasis and the metabolic balance that is essential to support cell function can also lead to disease.

Importantly, it is becoming increasingly appreciated that inflammatory processes are associated with alterations in mitochondrial function and cellular metabolism, and are heterogeneous with respect to the cell types and molecular mediators that are involved, constituting a spectrum of responses that go beyond infection to include responses to tissue stress or malfunction (Chovatiya and Medzhitov, 2014; Medzhitov, 2008; Okin and Medzhitov, 2012). Chronic, low-grade inflammation positively correlates with age and is associated with most degenerative diseases of the elderly (Chung et al., 2009; Franceschi et al., 2007; Howcroft et al., 2013; Pawelec et al., 2014). In addition, strong inflammatory responses are a common denominator of all major diseases in humans, including diabetes, cardiovascular disease, neurodegenerative disease and cancer (Medzhitov, 2010; Okin and Medzhitov, 2012).

For these reasons, addressing the processes of cellular differentiation and inflammation in the context of ageing may provide significant insight into age-associated disease. This review will discuss how these two processes – differentiation and inflammation – are intimately related to determine heath or disease, with mitochondria playing a central role (Fig. 1). It will be argued that (1) metabolism is the core language that cells use to process the different intracellular and extracellular signals; (2) differentiation is an interpretation of that language, an acquisition of specialized functions towards complexity; and (3) inflammation is a reaction to stress that alters metabolism, meant for adaptation and recovery from adversity, but that, if continued or exacerbated, can lead to disease by compromising cell function. This review will first address the implications of differentiation, inflammation and metabolism for cellular function in the context of ageing, and later examine the practical interpretation of this conceptual interplay in the specific context of the brain.

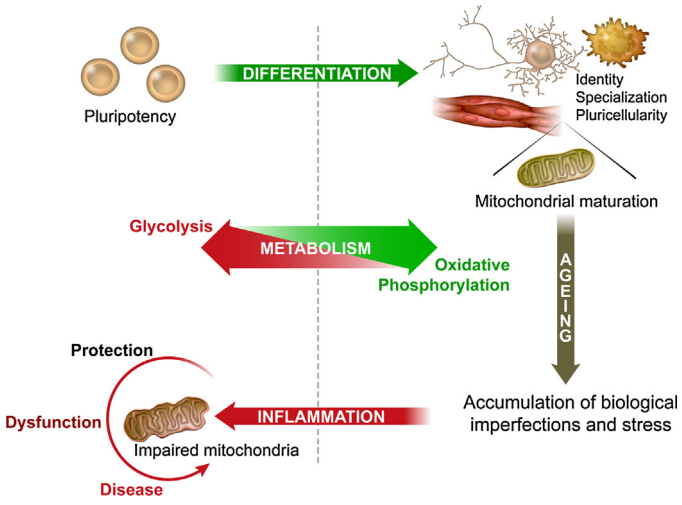

Fig. 1. The relationship between metabolism, differentiation and inflammation determines health and disease during ageing. When differentiating, cells acquire identity (specialized functions). The transition from pluripotent stem cells to differentiated somatic cells is characterized by a metabolic shift from glycolysis towards an increase in oxidative phosphorylation (OXPHOS). This shift is accompanied by changes in mitochondrial morphology and composition (mitochondrial maturation), to ensure an adequate supply of energy necessary to support specialized functions. With differentiation, cells also commit themselves to accumulate biological imperfections with ageing. As a response to the stress caused by the accumulation of these imperfections, cells can mount inflammatory responses that affect mitochondrial function. With age-associated inflammation, OXPHOS is reduced and cells may increase aerobic glycolysis. This metabolic response can, in part, confer protection but will become detrimental to cell function if persistent and uncontrolled.

2. Differentiation

2.1. Acquiring identity

While shifting from stemness to differentiation, cells lose their immortality status in order to gain identity, where identity is defined as the acquisition of specialized functions that altogether sustain the complexity of the organism.

The processes that mediate the amplification of a single fertilized cell into the maturity of a complex multicellular organism are complex and require restricted programmes meant to ensure both fidelity and functionality. Every time a cell divides, new components are synthesized and the whole physical structure is re-organized. This can pose a challenge to function and cellular interactions, and the dynamics of cellular division could thus conflict with that of differentiation. To slow down and halt proliferation may have allowed cells to integrate specific functions and to establish complex interactions with each other, building upon complexity. As such, most of the cells of the human body are in a functional non-proliferative G0 phase (Alberts et al., 2007). The reversibility of this state varies with different cell types. For instance, while neurons are terminally differentiated, many other cell types may only transiently withdraw from the cell cycle when necessary (Alberts et al., 2007).

Complex multicellular organisms appear to have evolved in such a way that most of their cells do not have a descendent lineage, but instead, ensure that the success of the organism, as a species, is reflected in the transmission of its germ line. In this context, to understand why embryonic stem cells and/or germ cells may represent an immortal line as opposed to somatic cells is to understand how the process of ageing may be related to that of differentiation.

Ageing in humans, as in other eukaryotes, might well be interpreted in light of the complexity acquired with the evolution of highly developed multicellular systems. Simple prokaryotic life does not form highly complex relationships, as found in eukaryotes.