ELSEVIER

The role of the 14-3-3 protein family in health, disease, and drug development

Yasaman Aghazadeh[1,2] and Vassilios Papadopoulos[1,2,3,4]

[1] The Research Institute of the McGill University Health Centre, Montreal, QC H4A 3J1, Canada
[2] Department of Medicine, McGill University, Montreal, QC H3G 1A4, Canada
[3] Department of Pharmacology and Therapeutics, McGill University, Montreal, QC H3G 1Y6, Canada
[4] Department of Biochemistry, McGill University, Montreal, QC H3G 1Y6, Canada

14-3-3 proteins regulate intracellular signaling pathways, such as signal transduction, protein trafficking, cell cycle, and apoptosis. In addition to the ubiquitous roles of 14-3-3 isoforms, unique tissue-specific functions are also described for each isoform. Owing to their role in regulating cell cycle, protein trafficking, and steroidogenesis, 14-3-3 proteins are prevalent in human diseases, such as cancer, neurodegeneration, and reproductive disorders, and, therefore, serve as valuable drug targets. In this review, we summarize the role of 14-3-3 proteins in normal and disease states, with a focus on 14-3-3γ and ε. We also discuss drug compounds targeting 14-3-3 proteins and their potential therapeutic uses.

Introduction

14-3-3 proteins are crucial regulators of intracellular signaling pathways. Upon interacting with their target protein, 14-3-3 proteins alter its activity, modifications, and intracellular localization [1]. The functions of 14-3-3 proteins can be categorized from two different viewpoints: isoform and tissue specificity.

Owing to their high degree of homology, researchers initially thought that 14-3-3 isoforms were redundant and, in the absence of one 14-3-3 isoform, others would compensate. Indeed, a 14-3-3γ-knockout (K/O) mouse model showed no change in brain phenotype, where 14-3-3 proteins are most abundant [2]. In-depth studies of the 14-3-3 phylogenetic tree suggest that all isoforms evolved before the divergence of mammals and that the orthologs have a higher homology compared with isoforms of the same species, implying that 14-3-3 isoforms have unique and fundamental roles [3]. This hypothesis is supported by mass-spectrometry studies identifying unique networks for each 14-3-3 isoform [4]. 14-3-3-Isoform specificity was further confirmed by studies of 14-3-3 isoform-specific K/O mice that found various tissue-specific phenotypes [5]. Based on data provided by the two main online microarray databases (http://biogps.org and http://www.proteinatlas.org), we summarize the tissue-specific expression of 14-3-3 isoforms in Fig. 1.

Corresponding author: Papadopoulos, V. (vassilios.papadopoulos@mcgill.ca)

Certain 14-3-3 functions are similar in multiple tissues, because their target proteins are involved in global pathways. The global roles of 14-3-3 proteins can be divided into two categories: (i) cell cycle progression and apoptosis; and (ii) intracellular protein trafficking. Tissue-specific roles for 14-3-3 proteins are observed for those that target proteins in particular cell types, such as adipocytes, neurons, and testicular Leydig cells.

Functions of 14-3-3 family members

The cell cycle and apoptosis

Much work has been dedicated to understanding the role of 14-3-3 proteins in cell proliferation, growth, and apoptosis. Mitogenic signals promote proliferation through the rat sarcoma (Ras)/rapidly accelerated fibrosarcoma (Raf)/mitogen-activated protein kinase (MAPK) cascade [6] and activate downstream MAP Kinase Kinase Kinase proteins (MEKK) [7]. 14-3-3ε, ζ, and θ, respectively, regulate MEKK2 dimerization in mouse embryonic fibroblast cells [8], MEKK1 functions in human prostate adenocarcinoma cell lines [9], and phosphorylation-dependent activity of MEKK3 in human fibroblasts cell lines [10]. 14-3-3 proteins are also involved in cell growth and survival. Acting through the extracellular signal-regulated kinase (ERK) pathway, 14-3-3ζ, ε, and γ mediate the activation of rapidly accelerated fibrosarcoma (Raf), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and mitogen- and stress-activated protein kinases (MSK1/2) in many cell types,

1359-6446/© 2015 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.drudis.2015.09.012

Please cite this article in press as: Aghazadeh, Y., Papadopoulos, V. The role of the 14-3-3 protein family in health, disease, and drug development, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.09.012

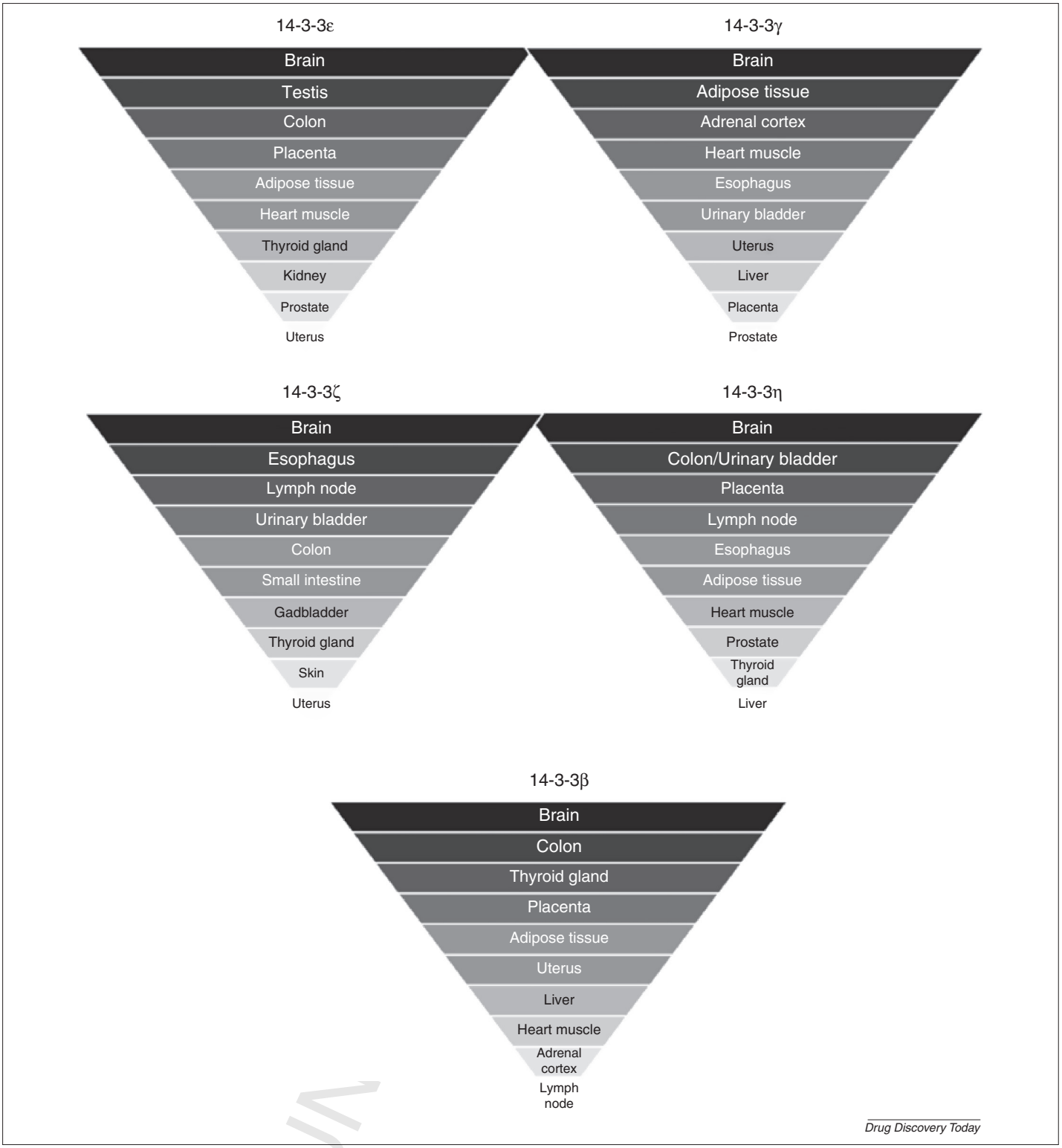

FIGURE 1

Differential expression levels of 14-3-3 isoforms in human tissues. 14-3-3 isoforms are shown in human tissues from highest to lowest expression levels as indicated by dark to light colors. Such differences suggest that there is tissue specificity for each isoform.

including hematopoietic stem cells and human breast, prostate, and fibroblast cell lines [11–15]. Downstream of the protein kinase B (PKB or Akt) pathway, 14-3-3ζ drives cell survival by inducing the phosphorylation and deactivation of B cell lymphoma 2 (Bcl-2)-associated death promoter (BAD), which leads to inhibition of apoptosis and promotes the cytosolic retention of Forkhead (FOXO) transcription factors, thus blocking the expression of downstream pro-apoptotic genes [11] (Fig. 2a).

Please cite this article in press as: Aghazadeh, Y., Papadopoulos, V. The role of the 14-3-3 protein family in health, disease, and drug development, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.09.012