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Review

Should I stay or should I go: β-catenin decides under stress

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ABSTRACT

Reactive oxygen species (ROS) are essential for efficient and proper execution of a large number of cellular processes including signalling induced by exogenous factors. However, ROS are highly reactive in nature and excessive or prolonged ROS formation can result in considerable damage to cellular constituents and is implicated in the onset of a large variety of diseases as well as in the process of ageing [reviewed in [1] T.M. Paravicini, R.M. Touyz, Redox signaling in hypertension, Cardiovasc. Res. 71 (2006) 247–258, [2] P. Chiarugi, From anchorage dependent proliferation to survival: lessons from redox signalling, IUBMB life 60 (2008) 301–307, [3] M. Valko, D. Leibfritz, J. Moncol, M.T. Cronin, M. Mazur, J. Telser, Free radicals and antioxidants in normal physiological functions and human disease, Int. J. Biochem. Cell Biol. 39 (2007) 44–84]. Management of ROS to prevent potential damage, yet enabling its signalling function is achieved through numerous enzyme systems e.g. peroxidases, superoxide dismutases etc. and small molecules e.g. glutathione that collectively form the cellular anti-oxidant system. The O-class of Forkhead box (FOXO) transcription factors regulates amongst others cellular resistance against oxidative stress [[4] Y. Honda, S. Honda, The daf-2 gene network for longevity regulates oxidative stress resistance and Mn-superoxide dismutase gene expression in *Caenorhabditis elegans*, Faseb J. 13 (1999) 1385–1393]. In turn FOXOs themselves are regulated by ROS and cellular oxidative stress results in the activation of FOXOs [[5] M.A. Essers, S. Weijzen, A.M. de Vries-Smits, I. Saarloos, N.D. de Ruiter, J.L. Bos, B.M. Burgering, FOXO transcription factor activation by oxidative stress mediated by the small GTPase Ral and JNK, EMBO J. 23 (2004) 4802–4812]. A prominent feature of ROS-induced FOXO activation is ROS-induced binding of β-catenin to FOXO [[6] M.A. Essers, L.M. de Vries-Smits, N. Barker, P.E. Polderman, B.M. Burgering, H.C. Korswagen, Functional interaction between beta-catenin and FOXO in oxidative stress signaling, Science (New York, NY) 308 (2005) 1181–1184, [7] M. Almeida, L. Han, M. Martin-Millan, C.A. O'Brien, S.C. Manolagas, Oxidative stress antagonizes Wnt signaling in osteoblast precursors by diverting beta-catenin from T cell factor- to forkhead box O-mediated transcription, J. Biol. Chem. 282 (2007) 27298–27305, [8] D. Hoogeboom, M.A. Essers, P.E. Polderman, E. Voets, L.M. Smits, B.M. Burgering, Interaction of FOXO with beta-catenin inhibits beta-catenin/T cell factor activity, J. Biol. Chem. 283 (2008) 9224–9230]. However, ROS affect many transcriptional programs besides that of FOXOs. Here, we discuss the recent progress in our understanding as to how ROS may regulate the interplay between some of the ROS-sensitive transcription factors through diverting β-catenin binding to these transcription factors. We propose that β-catenin acts as a key switch between the various ROS-sensitive transcription programs.

Contents

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1. Introduction

Within the process of reduction–oxidation reactions where O_2 is converted to H_2O, reactive oxygen species (ROS) are constantly formed as intermediate products. These intermediate ROS products consist either of short lived free radicals, characterised by unpaired electrons such as $O_2^{\cdot -}$, or nonradical derivatives such as hydrogen peroxide (H_2O_2), which for example is rapidly formed after conversion of $O_2^{\cdot -}$ by superoxide dismutases.

Within the cell several different sources of ROS production exist, most notably the mitochondria where ROS is produced as a side effect of cellular respiration, which is required for oxidative phosphorylation to efficiently generate ATP. However, ROS production is also induced by external stimuli such as growth factors, inflammatory cytokines, ionising radiation and chemotherapeutics. Treatment of cells with for example insulin, EGF or TNFα results in the production of significant amounts of H_2O_2 [9,10] through the regulation of specific NADPH oxidase (NOX) complexes present in the plasma membrane (reviewed in [11]). Inhibition of H_2O_2 production, for example through addition of catalase to cells, impairs signalling by these growth factors indicating that H_2O_2 production indeed functions within the context of normal growth factor signalling.

How H_2O_2 acts as a signalling molecule is slowly being understood. A paradigm in this respect is H_2O_2-mediated oxidation of cysteine residues. For example protein tyrosine phosphatases (PTPs), harbour a critical cysteine residue within their catalytic domain and oxidation of this cysteine by H_2O_2 inhibits phosphatase activity [12]. Consequently, H_2O_2 production initiated by growth factor signalling through for example tyrosine kinase receptors will result in enhanced receptor autophosphorylation and increased substrate phosphorylation due to H_2O_2-mediated PTP inhibition. This example clearly rationalises a role for H_2O_2 production in normal cell signalling. However, H_2O_2 mediated oxidation does not have to occur on cysteine residues but can also occur on other amino acids (e.g. tyrosine) and also does not always result in inhibition of protein activity. For example cysteine oxidation is required for c-src tyrosine kinase activity [13].

ROS is implied in the aetiology of a number of diseases such as cancer, diabetes, hypertension, chronic kidney disease and atherosclerosis [1–3]. Many of these diseases are known diseases of the elderly, and the possible involvement of ROS has led to the hypothesis that ageing in general occurs through the accumulation of oxidative damage to proteins, lipids, genomic and mitochondrial DNA. This has been coined "the free-radical theory of ageing" [14]. The role of genetic determinants affecting lifespan is studied in model organisms such as the nematode *Caenorhabditis elegans*. Here the lifespan affecting mutations in AGE-1, the homologue of phosphinositide-3 kinase (PI-3K), and/or DAF-2, the insulin receptor homologue, result in the activation of DAF-16, the nematode orthologue of mammalian FOXO. DAF-16/FOXO activation leads to the transcriptional upregulation of downstream target genes involved in cell cycle arrest, DNA repair, anti-oxidant resistance and apoptosis [4,15]. Loss of function of DAF-16 in *C. elegans*, and of FOXO in cultured mammalian cells results in a decreased resistance towards oxidative stress and in *C. elegans* this also leads to a decreased lifespan. Recently increased JNK signalling both in *C. elegans* and *Drosophila* was shown to also increase stress resistance and lifespan [16]. DAF-16/dFOXO is required for JNK to extend lifespan and stress resistance [17,18]. In agreement, previous work showed FOXO, more particularly FOXO4, to be directly phosphorylated by JNK and this correlated with increased nuclear localisation and transcriptional activity. This demonstrates that a ROS–JNK–FOXO pathway regulates stress resistance and can affect lifespan. Taken together these and other observations provide a strong support for a role of ROS in ageing, but also for JNK being a major ROS signalling intermediate.

An important mechanism of redox regulation of JNK proceeds through apoptosis signal-regulating kinase 1 (ASK1). ASK1 is a member of the mitogen-activated protein kinase kinase kinase (MAPKKK) superfamily and the activation of ASK requires homo-dimerisation [19]. Cysteine oxidation by ROS induces homo-dimerisation of ASK through a cysteine disulfide bridge rendering active ASK [20]. Consistent with this notion thioredoxin, which reduces cysteine disulfide bridges inhibits ASK activation [21]. Activation of ASK and binding of ASK to the JNK scaffold JIP3 [22], ultimately result in the activation of JNK. Besides FOXOs active JNK can phosphorylate directly a large number of transcription factors and thereby regulate their activity. Thus ROS-induced JNK-mediated phosphorylation constitutes a major pathway by which ROS regulates the transcription factor activity.

Recently, we described a ROS-dependent interaction between FOXO and β-catenin that appears to be evolutionary conserved [6]. In cells β-catenin is part of two major protein complexes [23]. First, β-catenin is complexed to α-catenin and the E-cadherin receptor and thereby β-catenin impacts on cell–cell adhesion. Second, β-catenin acts as a key player in the canonical Wnt pathway by interacting with, and activating the TCF (T cell factor) transcription factor. In *C. elegans* however it was shown that BAR-1 (the β-catenin orthologue) is also necessary for DAF-16-induced dauer formation, lifespan regulation, oxidative stress resistance and the expression of its target gene SOD-3 [6]. These findings illustrate the possibility that the function of β-catenin in transcription regulation is more versatile. Indeed, by now it has become clear that β-catenin interacts with a number of other transcription factors and besides TCF and FOXO it also interacts with HIF-1 and c-Jun [24,25]. It is noteworthy that these transcription factors are all regulated by ROS and the interaction with β-catenin enhances their activity, like was shown for the β-catenin/FOXO interaction. Under normal cellular conditions β-catenin, through Wnt signalling, is involved in cell proliferation and differentiation but under changed ROS conditions its function can shift to regulate transcription factors that support cell survival through increased stress resistance and ROS clearance. These findings may be taken to suggest that β-catenin is a pivot in reprogramming transcriptional activity following changes in ROS. Here, we will discuss the role of β-catenin in regulating different transcription factors following changes in ROS and the possible consequences thereof for understanding ageing and disease.

2. Wnt signalling towards β-catenin: the canonical pathway

Wnt proteins are secreted glycoproteins that influence the fate of nearby cells in several organs. Wnt proteins play a role in many biological processes such as embryonic development, stem cell maintenance [26] and cell proliferation [27]. Wnt signalling is initiated by Wnt-induced complex formation between the frizzled receptor and its co-receptor LRP. When bound these receptors activate dishevelled